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A Pharmacokinetic and Clinical Evaluation of Antimicrobial Drugs in Critically Ill Patients during Continuous Venovenous Haemodiafiltration (CVVHDF) therapy.

Volume 1

by

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being a thesis submitted for the degree of
Doctor of Philosophy

at
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under the supervision and direction of

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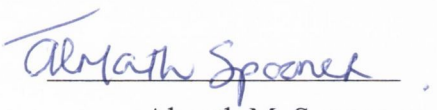
DECLARATION

This thesis is submitted by the undersigned to the University of Dublin, Trinity College, for examination for the degree of Doctor of Philosophy. It has not been submitted for a degree at any other university. I myself carried out all the practical work except where duly acknowledged. The library of University of Dublin, Trinity College, may lend or copy this thesis on request. This manuscript was written by me with the help of editorial advice from Prof. O.I. Corrigan.



Almath M. Spooner

Abstract

Critically ill patients are at risk from sepsis requiring antimicrobial therapy and acute renal failure, which may require extracorporeal renal replacement therapy. The objective of this study was to quantify and assess the impact of Continuous Venoveonous Haemodiafiltration (CVVHDF) therapy, a form of continuous renal replacement therapy, on the pharmacokinetics of commonly prescribed antimicrobial drugs. A preliminary audit undertaken as the first stage of this research identified a requirement for pharmacokinetic studies of a number of anti-infective agents during CVVHDF therapy. Two research strategies were used to address this objective. Initially a retrospective pharmacokinetic analysis of routinely monitored drug serum concentrations for patients treated with CVVHDF was used to obtain individual patient estimates of drug pharmacokinetic parameters. The drugs analysed were amikacin, gentamicin and vancomycin. Estimates of pharmacokinetic parameters obtained from the retrospective study of vancomycin agreed closely with published values from small prospective studies of vancomycin pharmacokinetics during Continuous Renal Replacement Therapy. In order to investigate drug disposition during CVVHDF further, a prospective pharmacokinetic and clinical study of antimicrobial drug therapy during CVVHDF was designed and implemented. In addition to examining routinely monitored antimicrobial drugs, an assay for ciprofloxacin determination in serum and CVVHDF effluent fluid was developed for the purposes of the prospective pharmacokinetic study. Ciprofloxacin differed from the other antibiotics examined, in that it has a significant non-renal component to its elimination. The prospective study allowed the measurement of multiple serum drug concentrations in a dosage interval and effluent fluid drug concentrations. Current drug dosing strategies for patients treated with CVVHDF were evaluated on the basis of these retrospective and prospective analyses. Both studies demonstrated significant drug clearance by CVVHDF. The retrospective study indicated that failure to adjust dosage regimens to account for this increased clearance capacity resulted in sub-therapeutic dosing of aminoglycoside antibiotics. The prospective study allowed analysis of the contribution of CVVHDF to total body clearance of each drug and an assessment of the validity of using therapeutic drug monitoring data to estimate pharmacokinetic parameters during CVVHDF.

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6. HPAI Annual Meeting. April 2005. (Poster Presentations)
   'An Investigation of the Pharmacokinetics of Antimicrobial Drugs during treatment with CVVHDF'. A. M. Spooner, O.I. Corrigan.
   'An Evaluation of drug use and the requirement for pharmacokinetic studies during CVVHDF' A. M. Spooner, O. I. Corrigan, M. B. Donnelly.
7. All-Ireland Schools of Pharmacy 27th Research Seminar, TCD. March 2005. 'An Evaluation of Drug Use and the Pharmacokinetic Basis for Drug Prescribing during CVVHDF'. A. M. Spooner, O. I. Corrigan.

List of Abbreviations

Abbreviation/Symbol	Definition
A	Intercept of the first exponential phase post bolus
α	Slope of first exponential phase post-infusion
A_1	The amount of drug in compartment number 1 (central compartment) at time t.
A_2	The amount of drug in compartment number 2 (tissue compartment) at time t.
AAA	Abdominal aortic aneurysm
ACE	Angiotenisn-convering enzyme
A_{nmin} is	the minimum amount in the body at τ after the nth dose.
A_{1max}	maximum amount in the 'body' or compartment immediately after the first dose
A_{nmax}	maximum amount in the 'body' or compartment immediately after the nth dose
APACHE	Acute Physiology and Chronic Health Evaluation
ARF	Acute renal failure
ATN	Acute tubular necrosis
AUC	Area under the curve
AUMC	Area under the first moment curve
B	Intercept of second exponential phase post-bolus
β	Slope of second exponential phase
BP	Blood pressure
C	Intercepts of third exponential phase post-bolus
C_a	concentration of the drug in the arterial circulation or the pre-filter concentration.
C_1	Concentration of drug in compartment number 1 at time t.
CAVH	Continuous arteriovenous haemodialysis
CAVHF	Continuous arteriovenous haemofiltration
C_{eff}	Drug concentration in CVVHDF effluent fluid
Cl_{CVVHDF}	Drug clearance due to CVVHDF
Cl_{creat}	Creatinine clearance due to CVVHDF
CrCl	Creatinine clearance
CV	Coefficient of variation
CVS	Cardiovascular system
CVVHD	Continuous venovenous haemodialysis
CVVHF	Continuous venovenous haemofiltration
CVVHDF	Continuous venovenous haemodiafiltration
CNS	Central nervous system

Corr.	Coefficient of correlation
C_{pmax}	maximum steady state concentration
C_{pmin}	minimum steady state concentration
CRRT	Continuous Renal Replacement Therapy
C_{ss} (serum/plasma)	Steady state blood concentration
Ct bolus/infusion	Concentration at any time t post-
CVP	Central venous pressure
D	Dose
DFR	Dialysis flow rate
D^{NORM}	Dose for patients with normal renal function
D^{REN}	Dose for patients with renal impairment
ESRF	End-stage renal failure
ESRD	End-stage renal disease
E^{SS}	steady-state creatinine urinary excretion rate
F	Bioavailability
fu	fraction of the drug unbound
GFR	glomerular filtration rate
HIT	heparin-induced thrombocytopenia
HPLC	High performance liquid chromatography
ICU	Intensive Care Unit
IBW	Ideal Body Weight
IHD	Intermittent haemodialysis
INR	International Normalised Ratio
IV	Intravenous
k model	elimination rate constant for 1-compartment
k_0	Zero order infusion rate
k_0^{NORM} function	Zero order infusion rate with normal renal
k_0^{REN} dysfunction	Zero order infusion rate with renal
k_{12}	First order rate constant for transfer of drug from compartment number 1 to compartment number 2.
k_{21}	First order rate constant for transfer of drug from compartment number 2 to compartment number 1.
k_{el}	First order rate constant for elimination of drug by all processes from compartment number 1
LFT	Liver function test
MAO	Monamine oxidase
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-resistant staphylococcus aureus
MSC	Model Selection Criterion

NCHD	Non-Consultant Hospital Doctor
NIDDM	Non insulin dependent diabetes mellitus
NSAID	Non-steroidal anti-inflammatory drug
NSS	Not statistically significant at a significance level of 0.05, unless otherwise indicated.
p	p-value
PK	pharmacokinetic
PD	pharmacodynamic
r^2	coefficient of determination
resp.	respiratory
RRT	Renal Replacement Therapy
RTA	road traffic accident
RTI	respiratory tract infection
SC	sieving coefficient
SD or sd	standard deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SPC	Summary of Product Characteristics
$T_{1/2}$	half-life
$T_{1/2\alpha}$	first phase elimination half-life
$T_{1/2\beta}$	second phase elimination half-life
T	dosage interval
TBC	total body clearance
TBW	total body weight
TDM	therapeutic drug monitoring
UF	ultrafiltrate
UFR	ultrafiltration rate
UV	ultraviolet
Vd	Volume of distribution (1-compartment model)
V_{dss}	Volume of distribution at steady state
V_1	Volume of compartment number 1.
Vd_{ext}	the extrapolated volume of distribution; defined by equation $Vd_{ext} = D/B$
VRE	Vancomycin-resistant enterococcus
WCC	White cell count

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Origin and Scope of Project

Critical illness and the presence of severe renal failure affect the pharmacokinetics of many drugs and dose modification is required in such a situation. There are widely varying data reported in the literature extrapolated from non-critically ill patients with renal failure and from critically ill patients without renal failure. The literature on drug pharmacokinetics in critically ill patients becomes more confusing when renal replacement is considered, in part due to the many methods of therapy used. Continuous Venovenous Haemodiafiltration (CVVHDF) is a form of Continuous Renal Replacement Therapy (CRRT) frequently used as an alternative to conventional haemodialysis in critically ill patients with Acute Renal Failure (ARF). This modality of renal replacement therapy is better tolerated in the hypotensive patient than other forms of replacement. However, relatively little clinical data is available regarding the clearance of commonly used drugs during CVVHDF and dose recommendations are often not underpinned by an evidence base. Data regarding the clearance of drugs by conventional haemodialysis cannot be accurately extrapolated to CVVHDF because of differences in the membranes used; differences in blood, ultrafiltrate, and dialysate flow rates; and the continuous nature of CVVHDF compared to the intermittent nature of haemodialysis. As patients receiving CVVHDF therapy are renally impaired, they are generally dosed on this basis in this ICU. However, there is evidence that drug pharmacokinetics, particularly elimination, may be altered during CVVHDF, resulting in subtherapeutic doses and ineffective therapy. Thus, the progress to therapies with greater clearances and the wider application of these techniques necessitates the reassessment of the impact of CRRT on drug pharmacokinetics.

Initially, an audit was carried out to investigate drug use, prescribing practice and pharmacokinetic considerations for critically ill patients receiving CRRT. This audit identified a need to characterise the behaviour of commonly prescribed antibiotics during CVVHDF therapy. Two research strategies were adopted to address this objective. Initially, a retrospective pharmacokinetic analysis of routine serum drug concentration data, measured as part of therapeutic drug monitoring, was undertaken. Subsequently, a prospective pharmacokinetic and clinical study was designed and undertaken. This prospective study allowed the measurement of frequent drug serum concentrations, the collection and analysis of CVVHDF effluent fluid and relevant clinical data. The drugs considered were vancomycin, amikacin, gentamicin and ciprofloxacin. Serum concentrations of vancomycin, amikacin and gentamicin are routinely monitored in the Hospital. For these drugs, the results of both retrospective and prospective analyses were compared. It was necessary to develop an assay and undertake analysis of ciprofloxacin concentrations in serum and effluent fluid, as part of this research. The data collated during the retrospective and prospective pharmacokinetic studies were used to reach conclusions on antimicrobial drug disposition and dosing strategies for use during CVVHDF.

Chapter 1: Introduction

1.1 Critical illness

1.1.1 Intensive Care Unit

Intensive care units are a vital component of modern health care. Intensive care is the term used to describe the highest level of patient management, care and treatment. This requires special expertise and a specially designated ward, with facilities for the critically ill and a team of specially trained staff. An intensive care unit (ICU) is a designated area offering facilities for the prevention, diagnosis and treatment of multiorgan failure. The level of care in the ICU is appreciably greater than on general wards, with more detailed observation and invasive treatment, which involve the efforts of a multidisciplinary team of doctors, nurses, pharmacists, physiotherapists, dieticians, technicians and others. Guidelines on the design of Intensive Care Units, equipment, services and staffing have been developed. The Intensive Care Society of Great Britain delineates minimum standards for an ICU, in its 'Standards for Intensive Care Units' (1). Design details for consideration include type, size and site of the ICU, patient areas, storage and supporting areas and equipment. In order to maintain the highest level of patient care, policies for the care of patients should be formulated and standardised. Clear cut administrative policies are vital, for example regarding access to the unit. There must be clearly defined policies for admission, discharge, management and referral of patients. The level of staffing depends on the type of hospital, but lines of responsibility must be clearly defined for all staff members. An ICU should have formal audit, peer review and quality assurance processes, together with on-going academic programmes.

1.1.2 Intensive Care Patient

Intensive Care Patients are patients with potentially recoverable conditions, who can benefit from more comprehensive observation and invasive treatment than can be provided safely in an ordinary ward or high dependency area. It is usually reserved for patients with threatened or established organ failure, often arising as a result or complication of an acute illness or trauma, or as a predictable phase in a planned treatment programme. If a patient has extra risk factors for general surgery, for example, age or co-morbidities, the patient may require post-operative intensive care. Specified criteria for admission to ICU have been defined (2). Intensive care is appropriate for:

(1) Patients requiring or likely to require advanced respiratory support alone;

(2) Patients requiring support of two or more organ systems;

(3) Patients with chronic impairment of one or more systems sufficient to restrict daily activities and who require support for an acute reversible failure of another organ system.

The unit will only admit patients whose lives are in imminent danger and in whom the immediate risk may be averted by active and often invasive therapeutic interventions and this should be reflected in a formal policy for admission and discharge. Generally, ICU patients suffer from respiratory failure and or/ circulatory dysfunction. Patients admitted to the Intensive Care Unit require active and aggressive therapy for appropriate treatment of a diagnosed condition or often life-support while a definitive diagnosis is made. In the critically ill patient, assessment of deranged physiology and immediate resuscitation must precede diagnostic considerations. At admission, classification by specialty according to primary dysfunction is rarely possible

and it is this initial diagnostic uncertainty and the need for immediate monitoring and physiological support that defines critical care medicine.

1.2 Pharmacokinetics in Pharmacy Practice

Pharmacokinetics is the application of the science and techniques of kinetics to drug behaviour in biological systems. In pharmacokinetics, the processes of drug absorption, distribution and elimination are characterised mathematically. Mathematical characterisation of these processes permits quantitative prediction of amounts and concentrations of drug in the body as a function of time and dosing regimen. The use of kinetic techniques to study drugs date back to the work of Widmark and Tandberg (3), who in 1928 published the first account of a one-compartment open model. Another description of pharmacokinetics is that is an attempt to understand the dynamics of drug absorption, distribution and elimination by studying simplified versions of the biological system. These simplified versions are models. By understanding the model, insights into the real biological system are achieved. Pharmacokinetic techniques are useful for a number of specific applications, in addition to providing an improved understanding of drug dynamics in biological systems. Specific applications important in pharmacy practice include:

1. Dosing regimen design, including calculation of infusion rates and multiple dose regimens to achieve a desired body level of drug.
2. Alteration of dosing regimens to compensate for certain pathological conditions that alter drug pharmacokinetics; e.g. renal failure, hepatic failure and congestive heart failure.
3. Measurement of drug bioavailability
4. Identifying and understanding the mechanisms of certain types of drug interactions.

The most commonly used models in pharmacokinetics are called compartment models. With compartment models, the body is assumed to behave with regard to drug pharmacokinetics as would one or more homogenous compartments. The real system is of course much more complex than the model. The assumptions involved in transforming the real system to the model include:

1. Instantaneous distribution
2. Linear distribution

The assumption of linear distribution allows the use of one tissue as a reference tissue. The dynamics of a drug can be studied in that tissue and those dynamics can be related to what is happening in all the other tissues. Our reference tissue is blood (serum) for two reasons:

1. It is relatively easy to take samples, as compared with liver and heart biopsies.
2. It is the one tissue that is in close contact with all the other tissues.

The number of compartments that comprise a model depends on several factors. The simplest model consists of one compartment. It is assumed that when a drug enters the body, it distributes instantaneously to all body tissues. There are times when two-compartment or even three-compartment models are needed instead of the one-compartment model. The decision of how many compartments to use in the model is made by considering the following factors:

1. Drug rate of equilibration among the tissues. If equilibration among one group of tissues is rapid and slow among another group, two compartments may be required.
2. Purpose of the model. How much detail is required? Dosing calculations may only require a one-compartment model, while

uncovering the mechanism of interaction may require a more detailed model.

3. Data available. Models are based on serum concentrations of drug after its administration. The greater the number of compartments, the greater the number of serum concentrations (data points) required. In the clinical setting, the number of serum concentrations available will often be limited for patient comfort, logistical and economic reasons.

Pharmacokinetic models lead to the development of mathematical equations that predict the time course of drug concentration or amount in one or more compartments. A compartmentalised system is only an approximation of a biological system because variations in physical distributions, non-homogeneity of the media and diffusion processes are all interrelated with chemical changes. Therefore, a 'compartment' is really an 'average' rather than an exact state, and is really a reflected characteristic of a system rather than an absolute one. The pharmacokinetic model is the equation or set of equations, which describe the proposed system. Linear pharmacokinetic equations all have either first order or zero order input rate constants, and first order distribution and elimination rate constants. The solution of the differential equations of linear pharmacokinetic models is polyexponential in form. The integrated equations can be generalised as:

$$C = \Sigma C_i e^{-\lambda i t} \qquad \text{(Equation 1.2.1)}$$

Where C is the blood concentration at time t, C_i is the ith coefficient, which may be positive or negative and λi is the exponent of the ith exponential term.

1.2.1 One Compartment Open Model

This model finds wide application in pharmacy practice. While the number of different routes for drug administration is relatively large, the kinetics of input are generally one of the following:

1. Instantaneous – drug in solution is administered directly into the blood by rapid intravenous injection. This is commonly termed 'i.v. bolus'.
2. Infusion – drug in solution is administered intravenously at a constant rate for a relatively longer period of time. When continued for a sufficiently long period of time, a constant concentration is achieved. The parameter used to denote an infusion is k_0. It is a zero-order rate constant that has units of amount of drug per unit time e.g. mg/hr.
3. Absorption – a rate constant, ka, is used to denote an absorption input.

1.2.2 One-Compartment Model: the I.V. Bolus case

As administration is instantaneous, the behaviour of the drug after administration is determined solely by processes of distribution and elimination. For this reason, i.v. bolus administration is commonly used when a pharmacokinetic model for drug disposition is being developed.

The assumptions of the one compartment open model with bolus intravenous injection (single dose) are:

1. The body is represented by a single compartment with volume V.
2. There is no distribution phase
3. A spike dose, D, is put instantaneously into the single compartment at time zero.
4. Unchanged drug is measured in plasma and the plasma concentration is assumed to be C at time t.

5. Loss from the 'body' is assumed to be first order and the rate constant is represented by k.

A proportionality constant, called the apparent volume of distribution (Vd) is used to characterise the size or capacity of the compartment. It is a proportionality constant because it relates the amount of drug in the compartment (A) to the concentration of drug in serum (C):

$A = Vd.\ C$ (Equation 1.2.2.1)

Drug may be eliminated from the body by biotransformation or excretion. In the development of pharmacokinetic models, elimination is generally assumed to follow first order kinetics. For the i.v. bolus case,

$dA/dt = -\ k.\ A_0$ (Equation 1.2.2.2)

The proportionality constant is k. It is termed the elimination rate constant and is a first order rate constant. It has units of $time^{-1}$.

The integrated form of this rate law is:

$A = A_0 e^{-kt}$ (Equation 1.2.2.3)

where A_0 represents the initial amount in the 'body' at time t=0.

This equation indicates that A declines exponentially with time from an initial concentration of A_0. To obtain an estimate of k from several values of A measured at different times, a semilog plot is used:

$\log A = \log A_0 - k.t / 2.303$ (Equation 1.2.2.4)

Thus, to estimate k:

$k = -2.303 slope$ (Equation 1.2.2.5)

A parameter used to convey the same equation as k is the biological half-life of the drug. The $t_{1/2}$ of a drug is the time required for elimination of 50% of the drug. It is inversely related to k. Metabolism, renal and biliary excretion are all

first order. Therefore the concept of a half-life is useful for these processes since it is independent of concentration.

As, $A_0/2 = A_0e^{-kt1/2}$ (Equation 1.2.2.6)

the half-life may be calculated from the rate constant from:

$t_{1/2} = 0.693/k$ (Equation 1.2.2.7)

By definition, $A^0 = D$ and $C = A/Vd$, hence

$C = C_{0.}e^{-kt}$ (Equation 1.2.2.8)

where $C_0 = D/Vd$.

For a one-compartment model, the pharmacokinetics after i.v. bolus administration are determined by only two parameters: Vd and k.

1.2.3 One compartment open model with bolus I.V. injection (Multiple Dose)

Many drugs are administered according to a multiple dosing regimen. The same assumptions hold as in the single dose case. It is assumed that a dose of size, D, is put instantaneously into the compartment at time t=0 and every τ hours where τ is the time between doses or the uniform dosage interval. A_{1min} is the minimum amount of drug in the 'body' or compartment at τ hours after the first dose and A_{nmin} is the minimum amount in the body at τ after the nth dose. A_{1max} and A_{nmax} are the maximum amounts in the 'body' or compartment immediately after the first and nth doses respectively. Then, the following equations apply:

$A_{1max} = D$ (Equation 1.2.3.1)

$A_{1min} = De^{-k\tau}$ (Equation 1.2.3.2)

The equations for maximum and minimum amounts and concentrations are:

$A_{nmax} = D\{1\text{-}e^{-nk\tau}/1\text{-}e^{-k\tau}\}$ (Equation 1.2.3.3)

and $C_{nmax} = D/V\{1\text{-}\ e^{-nk\tau}/1\text{-}e^{-k\tau}\}$ (Equation 1.2.3.4)

$A_{nmin} = D \{1-e^{-nk\tau}/1-e^{-k\tau}\} e^{-k\tau}$ (Equation 1.2.3.5)

and $C_{nmin} = D/V\{1- e^{-nk\tau}/1-e^{-k\tau}\} e^{-k\tau}$ (Equation 1.2.3.6)

At any time t after nth dose the equations for the amount and concentration are:

$A_n = D \{1-e^{-nk\tau}/1-e^{-k\tau}\} e^{-kt}$ (Equation 1.2.3.7)

and $C_n = D/V\{1- e^{-nk\tau}/1-e^{-k\tau}\} e^{-kt}$ (Equation 1.2.3.8)

After an infinite number of doses i.e n = ∞ ;

$C^{\infty}_{max} = (D/V)(1/1-e^{-k\tau})$ (Equation 1.2.3.9)

$C^{\infty}_{min} = (D/V)(e^{-k\tau} /1-e^{-k\tau})$ (Equation 1.2.3.10)

Thus, $C^{\infty}_{max} - C^{\infty}_{min} = D/V = C_0$ (Equation 1.2.3.11)

Hence, for this model, the difference between the maximum and minimum plasma/serum concentration at equilibrium will be D/V or C_0. This is independent of the value of k or $t_{1/2}$ and independent of the dosage interval. For the simple model where the dosage interval is made equal to the half-life the amount of drug in the body at equilibrium fluctuates between the unit dose D and twice the unit dose or 2D, and the maximum plasma/serum concentration is exactly twice the minimum plasma/serum concentration, according to equation :

$C^{\infty}_{max} / C^{\infty}_{min} = 2$ (Equation 1.2.3.12)

Hence an appropriate loading dose according to this model is a dose equal to twice the maintenance dose, which is given every τ hours when the dosage interval is made equal to the half-life of the drug. According to this model and the described dosage regimen, equilibrium conditions would be attained after the first dose or loading dose.

1.2.4 One Compartment Open Model with constant rate Intravenous Infusion (Single Dose)

The following equations are applicable to serum/plasma concentration data if this model applies:

$C = C_0 e^{-kt}$ (Equation 1.2.4.1)

where $C_0 = D/V$, and during a single infusion over τ hours

$C = [k_0 / V. k] \{ 1- e^{-kt}\}$ (Equation 1.2.4.2)

Where $0 \leq t \leq \tau$

After the infusion ceases,

$C = C_\tau . e^{-k(t-\tau)}$ (Equation 1.2.4.3)

Where $t \geq \tau$,

And $C\tau = [k_0 / V. k] \{ 1- e^{-k\tau}\}$ (Equation 1.2.4.4)

Also, $k_0 = D/\tau$. (Equation 1.2.4.5)

The equations indicate that during the infusion the concentration, C, increases exponentially, and after the infusion has ceased the concentration decreases exponentially, and in both cases the rate constant k is involved. If the infusion was not stopped but maintained equation 1.2.4.2 indicates that the concentration would approach the asymptotic concentration equal to k_0/VK.

1.2.5 One Compartment Open Model with constant rate Intravenous Infusion (multiple dose)

The following equations are applicable to blood concentration data where the one compartment open model with constant rate intravenous infusion (multiple doses) applies. Assuming infusions are administered over a period of t hours every τ hours, the maximum and minimum concentrations after the first infusion are given by the following equations;

$C_{pmax}^{1} = [k_0 / V. k] \{ 1- e^{-kt}\}$ (Equation 1.2.5.1)

$C_{min}^{1} = C_{max.}\, e^{-k(\tau-t)}$ (Equation 1.2.5.2)

where k_0 is the infusion rate, which is given by the following equation, where D is the dose administered:

$k_0 = D/t$ (Equation 1.2.5.3)

These equations indicate that during the infusion the concentration C increases exponentially and after the infusion has ceased the concentration decreases exponentially and in both cases the rate constant k is involved. To estimate k, the serum concentration time data is plotted on a semi logarithmic graph and the terminal points (after the infusion ceases) that appear to be distributed about a straight line are selected. To obey a one-compartment model, the terminal points should fall on one straight line. The following equation is used to obtain an estimate of k:

$k = \ln(Cp2/Cp1)/t$ (Equation 1.2.5.4)

The following method can be used to obtain an estimate of V; assuming that the concentration just at the time the infusion stops is C_T and that this was the first time point also used to estimate k, then the equation in the previous section applies and rearrangement gives:

$k_0/V = (C_T.k)/(1-e^{-kt})$ (Equation 1.2.5.5)

As the infusion rate, k_0, the duration of the infusion, t, and k, the elimination rate constant are known, an estimate of Vd can be obtained.

Total Body Clearance (TBC) is estimated from the product of k and Vd:

$TBC = k.Vd.$ (Equation 1.2.5.6)

Certain drugs are commonly administered by multiple intravenous infusions in hospitalised patients. A number of antibiotics, including vancomycin and the aminoglycosides, are given by this route. Drugs which cannot be given orally because of their absorption characteristics or drugs with a short half-life whose serum concentrations must be maintained within a narrow therapeutic range are candidates for this mode of administration. Administration by multiple constant-rate infusions rather than multiple intravenous boluses results in a smaller range of peak to trough serum concentrations for a given regimen.

1.2.6 Sawchuk and Zaske method (SZM) for Multiple Short Intravenous Infusions

Sawchuk and Zaske (4) proposed a general approach to developing dosing regimens for drug administration by multiple intravenous infusions. It involves utilising serum concentration-data obtained during any dosage interval for the calculation of the apparent distribution volume and the half-life in individual patients. These values are then used to individualise the dosing regimen where it is required to maintain serum concentrations of the drug within a desired range. Therefore, the method is useful for drugs for which desired peak and trough concentration ranges can be identified, such as vancomycin and the aminoglycoside antibiotics.

The SZM (Sawchuk and Zaske method) involves first obtaining direct estimates of the individual patient's pharmacokinetic parameters. The method then allows the estimation of appropriate dosing intervals and infusion rates to produce desired maximum and or minimum serum concentrations. These calculations are based on the estimated half-lives and distribution volumes, and on the choice of a convenient infusion period. This approach is applicable

where there are at least two timed drug serum concentrations available for any single dosage interval in a series of constant rate infusions.

The SZM is appropriate where the elimination pharmacokinetics are first order and can be represented by a one-compartment open model.

Assuming first-order elimination of drug in the one-compartment model, the equation which describes the change in serum concentrations, Cp, during constant rate infusion is:

$$dCp/dt = k_0/Vd - kCp \qquad \text{(Equation 1.2.6.1)}$$

where k_0 is the zero-order infusion rate, Vd is the apparent distribution volume and k is the first-order elimination rate constant.

At the end of any infusion period in a series of multiple intravenous infusions (whether at steady state or not), the serum concentration C_{pmax} is given by:

$$Cp_{max} = k_0/kVd\ (1-e^{-kt}) + Cp_0e^{-kt} \qquad \text{(Equation 1.2.6.2)}$$

Where t is the duration of the infusion and Cp_0 is the concentration in serum remaining from a previously administered dose. Rearrangement of equation gives

$$Vd = k_0/k \times \{(1-e^{-kt})/(Cp_{max}-Cp_0e^{-kt})\} \qquad \text{(Equation 1.2.6.3)}$$

The serum concentrations during the post-infusion phase is

$$Cp_{post} = Cp_{max}.e^{-k(t` - t)} \qquad \text{(Equation 1.2.6.4)}$$

where t` is the time taken from the beginning of that infusion.

Serum concentration-time data obtained during the post-infusion phase can thus be fitted to equation 1.2.6.1, giving estimates of k (or $t_{1/2}$) and Cp_{max}. These values can then be used to estimate the apparent Vd in equation 1.2.6.3. If data from other than the first infusion interval are used, the pre-infusion level (Cp_0) must also be known. If the patient is at steady state, however, an

estimate of this pre-infusion level can be made by the serum concentration measured (or predicted by equation 1.2.6.4) at the end of the infusion interval. Where multiple constant-rate infusions are administered for a fixed infusion period t, at fixed dosage intervals, τ, the infusion rate required to produce a desired maximum and/or minimum serum concentration at steady state can be calculated. For the aminoglycosides, it is necessary to achieve a target Cp_{max} concentration. The infusion rate required to produce the desired Cp_{max} is obtained from the equation:

$$k_0 = [k.\ Vd.\ Cp_{max}][(1-e^{-k\tau})/(1-e^{-kt})] \qquad \text{(Equation 1.2.6.5)}$$

If it is desirable to maintain concentrations above some minimum therapeutic level, as for vancomycin, the infusion rate required to produce the desired Cpmin is obtained from the following equation:

$$k_0 = [k.Vd.Cpmin]\ [(e^{k\tau} - 1)/(e^{k.t} - 1). \qquad \text{(Equation 1.2.6.6)}$$

Thus, the appropriate dose and dosage interval can be estimated from the rearranged equations:

Interval:

$$\tau_{new} = 1/k \text{ x } \ln(\text{Cpeak target/Ctrough target}) + \text{tin} \qquad \text{(Equation 1.2.6.7)}$$

Dose:

$$Dose_{new} = [Vd \text{ x Cpeak target x } k \text{ x tin x } (1-e^{kt})] / [S \text{ x } F \text{ x } (1-e^{k.\ tin}) \text{ x } e^{-kt1}] \qquad \text{(Equation 1.2.6.8)}$$

1.2.7 Two-compartment Open Model with Bolus Intravenous Injection

The use of a two-compartment model is generally not necessary in pharmacy practice situations where a pharmacokinetic problem is encountered. However, it is used extensively in the pharmacokinetic literature. A two-compartment model is appropriate when the concentration versus time curve after rapid i.v. bolus injection shows a distributive phase.

Drug administered by rapid i.v. bolus is assumed to distribute instantaneously throughout the first compartment, giving a C_0 of D_0/V_1. This concentration

then declines relatively rapidly due to both elimination and distribution. During the relatively rapid decline in drug serum concentrations, the amount of drug in the peripheral compartment is increasing. When 'distribution equilibrium' is achieved, the Cp curve begins to drop more slowly, as drug is leaving the central compartment only as a result of elimination.

The following symbolism is used for the two compartment model in this thesis:

k_{12} is the first order rate constant for transfer of drug from compartment number 1 to compartment number 2.

k_{21} is the first order rate constant for transfer of drug from compartment number 2 to compartment number 1.

k_{el} is the first order rate constant for elimination of drug by all processes from compartment number 1.

D is the dose.

A_1 = the amount of drug in compartment number 1 (central compartment) at time t.

A_2 = the amount of drug in compartment number 2 (tissue compartment) at time t.

C_1 = concentration of drug in compartment number 1 at time t.

V_1 = volume of compartment number 1.

Vd_{ext} = the extrapolated volume of distribution; defined by equation $Vd_{ext} = D/B$

The two-compartment model predicts that after an i.v. bolus, the concentration versus time curve will be biexponential:

$C_1 = Ae^{-\alpha t} + Be^{-\beta t}$ (Equation 1.2.7.1)

where $A = D(\alpha - k_{21})/V_1(\alpha - \beta)$ and $B = D(k_{21} - \beta)/V_1(\alpha - \beta)$

α and β are hybrid rate constants that are complex functions of k_{12}, k_{21} and k:

$\alpha = ½ [(k_{12} + k_{21} + k_{el}) + \{(k_{12} + k_{21} + k_{el})^2 - 4\, k_{21}\, k_{el}\}^{1/2}]$ (Equation 1.2.7.2)

$\beta = ½ [(k_{12} + k_{21} + k_{el}) - \{(k_{12} + k_{21} + k_{el})^2 - 4\, k_{21}\, k_{el}\}^{1/2}]$ (Equation 1.2.7.3)

The relative sizes of the two compartments are determined by k_{12} and k_{21}. The model is constructed so that

$k_{12}.\, V_1 = k_{21}.\, V_2$ (Equation 1.2.7.4)

V_1 is determined from D/C_1 after an i.v. bolus and V_2 is then calculated as $(k_{12}/k_{21})/V_1$. Thus, the larger k_{12} is relative to k_{21}, the larger V_2 is relative to V_1.

$A + B = C_0$ so

V_1 is obtained from $D/A + B$ (Equation 1.2.7.5)

The model parameters are obtained from A, α, B, β via the following series of calculations:

$k_{21} = (A\beta + B\alpha)/(A+ B)$ (Equation 1.2.7.6)

$k_{el} = \alpha\, (\beta/k_{21})$ (Equation 1.2.7.7)

$k_{12} = \alpha + \beta - k_{21} - k_{el}$ (Equation 1.2.7.8)

It is important to be able to use these values in the calculations that have been developed for the one-compartment model. The k_e for a two compartment model does not give the $t_{1/2}$ for the drug. Instead, β is analogous to k_e for a one-compartment model and

$t_{1/2} = 0.693/\beta$ (Equation 1.2.7.9)

This $t_{1/2}$ is referred to as the beta half-life or $t_{1/2\beta}$. It is the biological half-life of the drug and it is the time required for C to decline 50% during the post-distributive or β phase.

During the distributive α phase, drug elimination is accelerated since the drug is concentrated in the elimination compartment. The α half-life, $t_{1/2\alpha}$, is a measure of the length of the alpha phase; 3.3 ($t_{1/2\alpha}$) is a good estimate of the duration of the α phase.

$t_{1/2\alpha} = 0.693/\alpha$ (Equation 1.2.7.10)

The volume of distribution is a relatively complex term in two-compartment models. The apparent volume of distribution during the β phase is termed Vd_{β} and it can be used to calculate D from Cp during the β phase. This volume is also called Vd_{area} since it is calculated from the area under the C vs. t curve.

$Vd_{area} = (\alpha/k_{21})V_1 = (k_{el}/\beta)V_1 = V_1(\alpha - k_{el})(k_{21} - \beta)$ (Equation 1.2.7.11)

Mean plasma clearance = $Vd_{area} .\beta = V_1 . k_{el}$ (Equation 1.2.7.12)

By definition, $Vd_{ext} = D/B$, thus

$Vd_{ext} = (\alpha - \beta) / (k_{21} - \beta). V_1.$ (Equation 1.2.7.13)

By general definition:

$V_{dss} = [\alpha + \beta - k_{el} / k_{21}] V_1$ (Equation 1.2.7.14)

The TBC (Total Body Clearance) can be calculated from either:

$TBC = k_e . V_1$ (Equation 1.2.7.15)

$TBC = \beta . V_{\beta}$ (Equation 1.2.7.16)

1.2.8 Two-compartment model approach for multiple short intravenous infusions

The model described in the previous section describes the case for a two compartment open model with Bolus I.V. injection. In the ICU setting, many drugs are administered as multiple dose short infusions. Post-infusion data must be converted to the equivalent i.v bolus case, before applying the equations associated with the i.v. bolus model. Computer fitting of post-constant rate intravenous infusion data provides an equation of the form (5):

$Cp = \Sigma Y_i e^{-\lambda i t}$ (Equation 1.2.8.1)

Since the infusion time, T, and the λ_i values are known, then the coefficients corresponding to bolus intravenous injection can be calculated as follows:

$C_i = \lambda i T Yi / e^{+\lambda i T} - 1$ (Equation 1.2.8.2)

Then the corresponding equation for bolus intravenous injection can be written as:

$$Cp = \Sigma C_i e^{-\lambda i t} \qquad \text{(Equation 1.2.8.3)}$$

All the equations for bolus intravenous injection can then be applied to obtain Cl, Vdext etc.

1.2.9 Non-compartmental Approaches to Pharmacokinetic Data Analysis

For many applications, it is not necessary to assume/demonstrate that a specific structured (compartmental/physiological) model is valid. Generally applicable relationships and methods are useful adjuncts to compartmental modelling approaches and compartmental modelling and non-compartmental methods are not mutually exclusive. The general approach for using non-compartmental methods is to identify general properties of many pharmacokinetic systems e.g. presence of a terminal monoexponential region in the plasma concentration time curve. These properties are then expressed in mathematical terms. The resulting mathematical expressions are then exploited to address specific applications, for examples, to derive equations/methods for estimation of descriptive summary parameters such as clearances and volumes of distribution.

In the case of intravenous administration (F=1), TBC can be expressed using non-compartmental methods by the equation:

$$Cl = Dose_{iv}/AUC_{iv} \qquad \text{(Equation 1.2.9.1)}$$

Volume of distribution can be expressed in the form of V_1 (Volume of the central compartment), V_Z (V_β, V_{area}) (V during the terminal monoexponential phase) and V_{SS} (V at steady state) using the following equations:

For an i.v. bolus:

$$V_1 = D_{bol}/C_{bol(0)} \qquad \text{(Equation 1.2.9.2)}$$

$$Vz/F = D/\lambda_Z . AUC \qquad \text{(Equation 1.2.9.3)}$$

and for a constant rate infusion;

$Vss = D_{bol}AUMC_{bol}/AUC^2_{bol}$ (Equation 1.2.9.4)

where AUMC is the Area under the first Moment of the plasma concentration curve.

The terminal elimination rate constant (λ_z) is the exponential coefficient associated with the terminal monoexponential phase of the plasma/serum concentration time course i.e. the value of λ_z when;

$C_t = C_z e^{-\lambda z.t}$, $t \geq t_z$ (Equation 1.2.9.5)

The terminal elimination half-life of the drug ($t_{1/2}$) is the time required for the plasma/serum concentration to decrease by half during the terminal monoexponential phase:

$T_{1/2} = 0.693/ \lambda_z$ (Equation 1.2.9.6)

The most common approach to noncompartmental pharmacokinetic parameter estimation is to calculate $AUC_{0\text{-}tlast}$ using the trapezoidal rule. Then,

$AUC_{0\text{-}tlast} = C_{tlast}/ \lambda_z$ (Equation 1.2.9.7)

where C_{tlast} and λ_z are estimated by fitting a monoexponential function to the terminal portion of the concentration time curve.

V_{SS} for a multiple dose short infusion is estimated (6) as

$V_{ss} = \text{Dose} \times [AUC_{0\text{-}tlast} + t_{last} \times C_{tlast}/\lambda_z]/(AUC_{0\text{-}tlast})^2$ (Equation 1.2.9.8)

1.3. Pharmacokinetic alterations in the critically ill

Physiological changes in critically ill patients can significantly alter the pharmacokinetics of drugs used in their treatment. Studies investigating specific changes in drugs in critically ill patients are limited. Most pharmacokinetic studies are performed in healthy volunteers or in patients with a specific disease state who are not critically ill. Critically ill patients are highly dynamic and often have multiorgan dysfunction potentially altering all aspects of drug therapy.

1.3.1 Distribution

The Volume of Distribution (Vd) for many drugs increases in the critically ill, possibly due to an expanded extracellular fluid volume and changes in the concentrations or characteristics of binding proteins (7,8). The systemic inflammatory response syndrome (SIRS) commonly present in critically ill patients is associated with an increase in extravascular fluid volume. This phenomenon, commonly referred to as 'third spacing' is partially due to the release of cytokines in response to sepsis, trauma or burns. Cytokines alter the normal capillary permeability, facilitating leakage of protein and fluid into the extravascular space (9).

Hypoalbuminaemia is common in critical illness due to deceased hepatic albumin synthesis and increased extravascular deposition (9). The resulting relative lack of colloid oncotic pressure in the intravascular space allows increased efflux of plasma volume into the interstitial space, resulting in oedema. Vigorous fluid resuscitation can also exacerabate peripheral and pulmonary oedema. Thus, the Vd of medications that are contained primarily within the intravascular space or that are highly plasma protein bound increases.

Many acidic drugs bind to albumin which forms the largest fraction of plasma proteins. Severe disease processes often cause a fall in the serum concentration

of albumin, which may increase the concentration of unbound active drug. Although this could potentially increase the risk of toxicity, the larger free fraction is then available for hepatic extraction and renal excretion which may diminish any increased pharmacodynamic effects. Additionally, it has also been suggested that the idea that only the free unbound fraction of the drug is available to enter the interstitial space and interact with the target tissue, may not be completely applicable to critically ill patients. Agents that exhibit a high degree of protein binding may display increased binding in the interstitial space, due to concomitant leakage of albumin. Therefore, although the tissue concentrations of the total drug (bound and unbound) may be elevated; a disproportionate fraction is bound and so is pharmacologically inactive. For this reason, therapeutic drug monitoring should measure the free drug concentration. In addition, fluid status can be highly variable in a critically ill patient with renal failure, leading to changes in a drug's Vd. Accumulation of fluid in patients with ARF can result in lower drug concentrations (9). In general, obesity will increase the Vd for lipophilic medications (10).

1.3.2 Metabolism

The alterations in drug metabolism seen in critically ill patients are dependent on the extraction ratio of the drug, the phase of critical illness and the patient's co-morbidities. Reasons for impaired metabolic function in critically ill patients include direct damage to the liver (cirrhosis), decreased blood flow to the liver (shock, elderly), or a result of concurrent medication (e.g. enzyme inducers or inhibitors) (11, 12, 13). Inflammatory medications such as tumour necrosis factor and interleukin-6 have the ability to inhibit cytochrome CYP450 enzymes. Thus patients with SIRS (Systemic Inflammatory Response Syndrome) may have acutely diminished metabolic capacity and resulting increased serum drug

concentrations. Low serum concentrations of albumin allow a higher percentage of highly protein-bound mediations to be unbound and available for metabolism. α_1-Acid glycoprotein is an acute phase protein, whose concentration increases after acute stress such as trauma, surgery or severe illness. It is the major binding protein for many alkaline drugs and may decrease the fraction unbound and subsequent hepatic metabolism (7).

1.3.3 Elimination

Drug excretion is the most crucial pharmacokinetic parameter pertaining to the development or avoidance of toxicity. The kidneys are principally responsible for elimination of unchanged drug and hepatic metabolites. Glomerular filtration, tubular secretion and reabsorption are the modes of renal excretion. Alterations in renal perfusion and function during critical illness are common and may cause variations in drug elimination. The early stages of sepsis, burn, head injury and trauma are typically described as 'hyperdynamic' and are usually accompanied by increased cardiac output and an associated increase in (Glomerular Filtration Rate) GFR. This may result in increased drug clearance and higher dose requirements. The corollary of this is that patients in shock who have not been adequately resuscitated or with congestive heart failure or in the late stages of shock or sepsis may have decreased drug clearance (14). Serum creatinine and calculated estimates of creatinine clearance are often unreliable due to changes in body composition, immobility and rapid muscle breakdown. Studies of drug elimination during critical illness have reported highly variable results and in practice many drugs will have large interindividual variability during critical illness and are dependent on the existence of prior renal disease and current renal perfusion. Renal dysfunction and treatment with Renal Replacement Therapy will further impact on drug pharmacokinetics and drug dosing in critical illness.

For these reasons, individualised therapeutic drug monitoring is advisable for those agents for which it is feasible.

1.4. Acute Renal Failure

1.4.1 Definition

Acute Renal Failure (ARF) describes a syndrome characterised by a rapid decrease in the kidney's ability to eliminate waste products, concentrate urine and conserve electrolytes. This loss of excretory function is clinically manifested by the accumulation of end products of nitrogen metabolism, urea and creatinine, which are routinely measured in ICU patients. Other typical clinical manifestations include decreased urine output, accumulation of non-volatile acids and an increased potassium concentration. Depending on the criteria used to define its presence, ARF has been reported to occur in 15-20% of ICU patients (15). Acute renal injury such as albuminuria, loss of small tubular proteins, inability to excrete a water, sodium or amino acid load is extremely common in critically ill patients.

1.4.2 Monitoring of renal function

Monitoring of renal function is commonly reduced to assessment of Glomerular Filtration Rate (GFR) by the measurement of serum urea and creatinine concentrations. These waste products are insensitive indicators of GFR and are influenced by nutrition, muscle injury, drug therapy such as the use of steroids or the presence of gastrointestinal blood. They become abnormal only when more than 50% of GFR is lost and they do not reflect dynamic changes in GFR. They are also heavily altered by aggressive fluid resuscitation. For example, in the case of a patient with decreased urea generation due to poor nutrition or to liver disease, manifestations of the uremic syndrome may appear when the serum urea nitrogen level is well below 18mmol /l (16). However, the use of creatinine

clearance increases the accuracy of renal function assessment and this is the primary measure used. Preferably, it should be determined from urine collection rather than from serum creatinine levels because formulas estimating clearance from the serum creatinine level generally assume steady state conditions, which as a rule do not hold in this setting. In addition to altered creatinine concentrations, other lab values may change suddenly (within a few days to 2 weeks): urinalysis may be abnormal; BUN (Blood urea nitrogen) may increase suddenly, serum potassium levels may be increased, arterial blood gas may show metabolic acidosis. This disease may also alter the results of the other tests, for example, 25-hydroxy Vitamin D, amylase, serum calcium, serum sodium, ESR, amongst others. Approaches to and factors affecting the assessment of renal function will be further discussed in Section 1.5.

1.4.3 Clinical Classification of ARF

One approach to the aetiological diagnosis of ARF is to classify its causes according to the source of renal injury:

1. Pre-renal renal failure is the most common form of ARF in the ICU. It is characterised by diminished renal blood flow. The kidney malfunctions primarily because of systemic factors, which impair renal blood flow and decrease GFR, or alter intraglomerular haemodynamics and thereby also decrease GFR. It is due to inadequate renal perfusion caused by hypotension (e.g. Congestive Heart Failure, sepsis), circulatory volume depletion (e.g. haemorrhage) or renal blood supply obstruction. The primary agents that cause pre-renal acute renal failure are angiotenisn-convering enzyme (ACE) inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs). Diminished renal blood flow causes ischaemia in the renal parenchyma and this may cause acute

tubular necrosis (ATN), if the ischaemia is prolonged. Early restoration of renal blood flow should shorten the ischaemic time and prevent parenchymal injury. The keys to therapy are treating the underlying disorder, maintaining euvolemia and eliminating offending agents.

2. Parenchymal renal failure is used to define a syndrome where the principal source of damage is within the kidney and where typical structural changes can be seen using microscopy. Disorders that affect the glomerulus or the tubule can be responsible. Glomerulonephritis is characterised by hypotension, proteinuria and hematuria. The two types of glomerulonephritis that are gnereally associated with acute renal failure are rapidly progressive glomerulonephritis and acute proliferative glomerulonephritis. The latter form occurs in patients with postinfection conditions such as bacterial endocarditis. Rapidly progressive glomerulonephritis can be a primary disorder, or it can occur secondary to systemic disease (e.g. systemic lupus erythematosus, small-vessel vasculitis, Goodpastures's syndrome). Many drugs can cause interstitial nephritis and nephrotoxins are particularly important in the hospitalised patient. The most common nephrotoxic drugs affecting ICU patients are radiocontrast agents, aminoglycosides, amphotericin, non-steroidal anti-inflammatory drugs, beta-lactam antibiotics, sulphonamides, acyclovir, methotrexate, cisplatin, cyclosporine A and tacrolimus (17). NSAIDs cause renal arteriolar vasoconstriction by inhibiting normal prostaglandin-induced vasodilation. In hypovolaemic patients this seriously reduces renal blood flow and GRF. NSAIDs also contribute to ARF in patients with pre-existing renal impairment and those using diuretics (e.g. cirrhosis).

Radiocontrasts, cyclosporine and amphotericin cause vasoconstriction, whereas aminoglycosides and cephalosporins are direct tubular toxins. ACE inhibitors block the angiotensin-mediated efferent arteriolar vasodilation that maintains GFR. Many drugs cause allergic tubulointerstitial nephritis (e.g. antibiotics, diuretics).More than one third of patients (17) who develop ARF in ICUs have chronic renal dysfunction due to factors such as age-related changes, long-standing hypertension, diabetes or atheromatous disease of the renal vessels. It may manifest as a raised serum creatinine but this is not always the case. Often, what may seem to the clinician to be a relatively trivial insult (e.g. administration of a nephrotoxin), which does not fully explain the onset of ARF in a normal patient is sufficient to unmask lack of renal function reserve in a patient with chronic renal dysfunction.

3. Hepatorenal syndrome is a form of ARF that occurs in the setting of severe liver dysfunction in the absence of other known causes of ARF. Typically, it presents as progressive oliguria insensitive to diuretics or fluids. Its pathogenesis is not well understood but appears to involve severe renal vasoconstriction. However, in patients with severe liver disease other causes of ARF are more common. These include sepsis, parancentesis-induced hypovolaemia, raised intra-abdominal pressure due to tense ascites, diuretic-induced hypovolaemia, lactulose-induced hypovolaemia, alcoholic cardiomyopathy, and any combination of these. The avoidance of hypovolaemia by albumin administration in patients with spontaneous bacterial peritonitis has been shown to decrease the incidence of renal failure in a randomised controlled trial

(18). Recent uncontrolled studies suggest that vasopressin derivatives (omnipressin) may improve GFR in this condition (19).

4. Rhabdomyolysis-associated ARF accounts for about 5-10% of cases of ARF in the ICU, depending on its setting (17). Its pathogenesis involves pre-renal, renal and post-renal factors. It is now typically seen following major trauma, drug overdose with narcotics, vascular embolism, and in response to a variety of agents which can induce major muscle injury.
5. Post-renal renal failure is caused by urinary tract obstruction. Resulting back-pressure inhibits GFR and causes ischaemia. ARF only occurs if both kidneys are obstructed. Obstruction to urine outflow is the most common cause of function renal impairment in the community, but is uncommon in the ICU. The primary causes of post-renal acute renal failure include bladder neck obstruction from an enlarged prostate, ureteric obstruction from pelvic tumours or retroperitoneal fibrosis, papillary necrosis or large calculi.

1.4.4 Pathogenesis of Acute Renal Failure

The pathogenesis of obstructive ARF involves several humoral responses as well as mechanical factors. The pathogenesis of parenchymal renal failure is typically immunological. It varies from vasculitis to interstitial nephropathy and involves a complexity of immunological mechanisms. The pathogenesis of pre-renal ARF is of most significance in the ICU. Several mechanisms play a role in the development of renal injury:

- Ischaemia of outer medulla with activation of the tubulo-glomerular feedback
- Tubular obstruction from casts of exfoliated cells

- Interstitial oedema secondary to back diffusion of fluid
- Humorally mediated afferent arteriolar renal vasoconstriction
- Inflammatory response to cell injury and local release of mediators
- Disruption of normal cellular adherison to the basement membrane
- Radical oxygen species-induced apoptosis
- Phosholipase A2 induced cell membrane injury
- Mitogen-activated protein kinases-induced renal injury

In septic patients with hyperdynamic circulations, there may be adequate global blood flow due to the kidney but intra-renal shunting away from the medulla causing medullary ischaemiai, or efferent arteriolar vasodilatation causing decreased intraglomerular pressure and thus decreased GFR.

1.4.5 Management of Acute Renal Failure

The principles of management of established ARF are the treatment or removal of its cause and the maintenance of physiological homeostasis while recovery takes place.

Initial treatment should focus on correcting fluid and electrolyte balances while the cause of acute renal failure is being sought. Therapy for acute renal failure is directed at treating the underlying causes, correcting fluid, electrolyte and uremic abnormalities, and preventing complications, including nutritional deficiencies.

Nutritional support must be started early. The main electrolyte disturbances in the acute setting are hyperkalemia and acidosis. The aggressiveness of treatment depends on the degree of hyperkalaemia and the changes seen on the electrocardiogram. Hyperkalaemia must be promptly treated, by temporarily shifting potassium into the intracellular compartment, either with intravenously administered insulin and dextrose, the infusion of bicarbonate if

acidosis is present, the administration of inhaled salbutamol, or all of the above together. If the true mean serum is > 7mmol/l or electrocardiographic signs of hyperkalaemia appear, calcium gluconate is also administered. The above measures are temporary actions while renal replacement therapy is being set up. The presence of hyperkalaemia is a major indication for the immediate institution of renal replacement therapy. Metabolic acidosis is almost always present and is treated with intravenously or orally administered sodium bicarbonate. Anaemia requires correction to maintain a haemoglobin > 70g/l (20). More aggressive transfusion needs individual patient assessment. Drug therapy must be adjusted to take into account the effect of the decreased clearances associated with loss of renal function. All medications should be reviewed, and their dosages should be adjusted based on the glomerular filtration rate and the serum level of drugs.

Stress ulcer prophylaxis is advisable and is usually based on H2-receptor antagonists or proton-pump inhibitors in selected cases. Fluid overload can be prevented by the use of loop diuretics in polyuric patients. However, if the patient is oliguric, the only way to avoid fluid overload is to institute renal replacement therapy at an early stage. Marked azotaemia (urea> 40 mmol/l or creatinine> 400 umol/l) is undesirable and should probably be treated with renal replacement therapy unless recovery is imminent or already under way and a return towards normal values is expected within 24 hours (21). The mortality of critically ill patients with ARF remains high (40-80% depending on case mix). Growing evidence suggests that better uraemic control and more intensive artificial renal support may improve survival by perhaps 30% (22, 23).

1.5. Assessment of Renal Function and Drug Dosage Regimens for Patients with Renal Insufficiency

1.5.1 Glomerular Filtration Rate

The design of the optimal dosage regimen for patients with renal insufficiency requires an individualised assessment and is dependent on the availability of an accurate characterisation of the relationship between the pharmacokinetic parameters of the drug and renal function, and an accurate index of the patient's renal function.

The kidneys remove drugs and endogenous by-products of metabolism from the body via several processes, including glomerular filtration, tubular secretion and tubular reabsorption. The rate of excretion of substances by the kidney is equal to the rate of filtration plus the rate of secretion minus the rate of reabsorption. The clearance of a drug as a result of glomerular filtration is dependent on the patient's Glomerular Filtration Rate (GFR) and the fraction of the drug not bound to plasma proteins. The assessment of glomerular filtration is fundamental to the management of drug therapy where clearance depends on renal function. Measurements of Glomerular Filtration Rate (GFR) are based on the renal clearance of a marker in plasma, expressed as the volume of plasma completely cleared of the marker per unit time. Markers used to measure GFR include endogenous compounds such as creatinine and urea, in addition to exogenous substances, including inulin and iothalamate. The ideal marker is endogenous, freely filtered by the glomerulus, neither reabsorbed nor secreted by the renal tubule and is eliminated only by the kidney. Clinically, the GFR can be approximated if the excretion rate of a 'freelly filtered' substance and its concentration in blood (serum/plasma) are known;

GFR = Excretion Rate/Concentration (Equation 1.5.1.1)

where excretion rate e.g. mg/min is the product of urine volume per unit of time and urine solute concentration and concentration is the plasma solute concentration at the midpoint of the urine collection interval.

1.5.2 Exogenous markers of renal function

Inulin is considered the 'gold standard' or 'freely filtered solute' of choice because it is freely filtered by the glomerulus and is neither reabsorbed nor secreted by the kidneys (24). It is metabolically inert and is only cleared by the kidneys. Its distribution is restricted to the extracellular fluid space, it is not bound to plasma proteins or tissues, and it easily passes through the pores of the glomerulus. Futhermore, inulin is not secreted, reabsorbed or metabolized in the renal tubules and is not eliminated by nonrenal routes (24). This agent can be safely administered intravenously and is the preferred measure of GFR when an accurate measure is critical. However, analysis of inulin is demanding and time-consuming. The procedure is complicated in that it requires the continuous intravenous infusion of inulin, the collection of a series of blood and urine samples at specified intervals and a reliable assay. As the analysis of inulin is technically demanding, a number of alternative methods of GFR assessment have been developed that use nonradioisotopic agents as the model solute. Radioactive marker solutes may also be used to measure GFR and these substances provide estimates of GFR that compare well with inulin.

1.5.3 Serum Creatinine and Creatinine Clearance

The most commonly accepted alternative to the administration of exogenous substances for the estimation of renal function is creatinine clearance (25-27). Commonly employed measures of renal function are based on creatinine and its usefulness lies in its clearance varying in direct proportion to the renal

clearance of many drugs. Creatinine is formed in the body from creatine and creatine phosphate in muscle. The rate of creatinine production is proportional to the amount of creatine in the body, which is in turn related to the lean body mass (28). It varies therefore with age and gender (29).The average creatinine production is 20mg/kg in 24 hours. Its apparent Vd is estimated to be 54% of body weight, both in normal subjects and in patients with renal failure. Dominquez et al (30) determined the mean half-life after oral administration as 2.4 hours. Chiou et al (31) determined the half-life to be 3.85 hours, but this estimate may be too high, due to an assumed Vd of 50L and the methodology applied. The value of the creatinine clearance is relatively constant in an individual. Normal subjects are at steady state, whereby the rate of production of creatinine is equal to the rate of excretion by the kidneys. If renal function is normal, creatinine is only eliminated by the kidneys and primarily by glomerular filtration. However, in patients with advanced kidney disease and therefore a low glomerular filtration rate, there is some slight secretion and metabolism of creatinine. In clinical practice, creatinine clearance is usually estimated form serum creatinine alone rather than from measurements in both plasma and urine. Apart from the extra analysis, involved, incomplete urine collection is a major problem resulting in the underestimation of creatinine clearance. Serum creatinine alone can be used because its daily production is matched by its elimination under normal circumstances. Consequently, serum creatinine is related to creatinine clearance by:

Serum creatinine = Rate of creatinine production/ Creatinine clearance

(Equation 1.5.3.1)

Once creatinine is released from muscle into plasma, it is eliminated almost exclusively by renal glomerular filtration. Any decrease in the GFR ultimately

results in a rise in serum creatinine until a new steady state is reached and the amount of creatinine eliminated per day equals the rate of production. Since the rate of creatinine production remains constant even when renal clearance decreases the serum creatinine must rise until the product of the clearance and the serum creatinine equals the rate of production.

Creatinine is distributed in total body water, is not bound to plasma proteins and is freely filtered at the glomerulus. These characteristics allow for the measured creatinine clearance to be a useful estimate of the GFR. Increases in the serum creatinine concentration are proportional to the decline in GFR and equations using creatinine have become the mainstay of the assessment of renal function. Despite this, the measurement of creatinine clearance (Cl_{cr}) may be imprecise even under the best of conditions. The following assumptions must be valid in order to consider creatinine clearance an accurate estimate of kidney function:

1. The daily anabolic production of creatine in the liver is constant.
2. The daily anabolic conversion of creatine to creatinine in striatal muscle is constant and other nonconstant sources of creatinine production do not exist.
3. Creatinine is freely filtered by the kidney and is not secreted or reabsorbed
4. The measurement of creatinine in serum and urine is accurate
5. The urine collection is complete.

The first assumption may not be valid in the malnourished or the critically ill. The synthesis of creatine from glycine, arginine and methionine in the liver may not be constant in malnourished patients or in those with hepatic

insufficiency. Thus, the first assumption may not be valid, especially in the critically ill (28).

A number of factors can affect the validity of the second assumption. The production and release of creatinine from muscle is directly proportional to lean body mass. Because lean body mass is difficult to estimate, Ideal Body Weight (IBW) has been frequently used as the index of muscle mass.

IBW males (kg) = 50 + (2.3kg/height in inches over 5ft) (Equation 1.5.3.2)

IBW females (kg) = 45.5 + (2.3kg/ height in inches over 5ft) (Equation 1.5.3.3)

Inter-individual variability in the relationship between ideal body weight and creatinine production is large. This is because muscle mass constitutes a reduced fraction of ideal body weight in certain individuals; thus, urinary excretion of creatinine is relatively reduced in females (32), neonates (33), the elderly (34) and in patients with muscular dystrophies and other muscle-wasting conditions (35). In contrast, muscle mass constitutes a larger fraction of ideal body weight in athletes (36). The rate of creatinine production and release also may not be constant in states of muscle destruction (e.g. rhabdomyolysis, major burn or trauma). The administration of drugs (e.g. trimethoprim) may also change the metabolic production of creatinine in muscle (37) and also the dietary intake of cooked meats provides an exogenous source of creatinine that may confound interpretation of the serum creatinine (38).

Creatinine, like inulin, is not protein bound and is freely filtered at the glomerulus. However, unlike inulin, it also undergoes active tubular secretion and thus is a less accurate measure of GFR. The extent of tubular secretion varies with renal function, which may introduce large errors in individuals with impaired renal function. In disease states that primarily affect the glomeruli

rather than the tubules e.g. acute glomerulonephritis and hypertension, the contribution of tubular secretion may become significant, resulting in an overestimation of GFR by creatinine clearance. Nonrenal elimination of creatinine by gut metabolism may become significant in patients with severe renal impairment and may account for up to 50% of creatinine elimination in ESRD patients (39). This would result in a lower than expected serum creatinine and an overestimation of the GFR.

On average, as patients age, their muscle mass represents a smaller proportion of their total weight and creatinine production is decreased. There are a number of equations that consider age, gender, body size and serum creatinine when calculating or estimating creatinine clearance for adults. The most common method used by Clinicians is probably the method suggested by Cockcroft and Gault (40).

Cl_{cr} for males (ml/min) = (140-Age)(Weight)/(72)(SrCrss)

(Equation 1.5.3.4)

Cl_{cr} for females (ml/min) = 0.85 x (140-Age)(Weight)/(72)(SrCrss)

(Equation 1.5.3.5)

where age is in years, weight is in kg and serum creatinine at steady state (SrCrss) is in mg/dL.

Irish Hospitals tend to use SI units for serum creatinine and the same relationship used to approximate creatinine clearance from serum creatinine can be expressed as

Cl_{cr} for males (ml/min) = 1.23 x (140-Age) x Weight/SrCrss

(Equation 1.5.3.6)

Cl_{cr} for females (ml/min) = 1.04 x (140-Age) x Weight/SrCrss,

(Equation 1.5.3.7)

where serum creatinine is reported in μmol/L.

There are a number of factors to consider when using the Cockcroft and Gault equation:

- The Cockcroft and Gault equation is only accurate when renal function is stable i.e. when serum creatinine is not fluctuating by more than 40μmol/day.
- It is inaccurate when serum creatinine values exceed 450μmol/L.
- It becomes inaccurate when GFR is less than 20ml/min.
- It is not valid in pregnancy
- It is not valid in children (can adjust the equation for body surface area)
- It is not valid in the very elderly
- It is inaccurate in patients with much decreased muscle mass (emaciated patients), highly muscular or obese patients.
- In patients with cirrhosis, the serum creatinine concentration is typically low and GFR is often underestimated.
- Rapid changes in creatinine production or renal function may not be reflected in serum creatinine for several days, and steady-state conditions are necessary for accurate estimation of Cl_{cr} using equations.

An alternative method of assessing renal function is the 24 hour urine collection, to estimate the amount of creatinine cleared by the kidneys in a 24-hour period. Although the collection process is often inconvenient to carry out and is prone to user error, it can give an accurate measurement of renal function. At the end of the collection period, a blood sample is taken to determine serum creatinine, or alternatively at a midpoint during the collection period.

$$GFR\ (ml/min) = C_{urine} \times V_{urine} / C_{serum} \qquad \text{(Equation 1.5.3.8)}$$

where C_{urine} is the urine creatinine concentration, V_{urine} is the volume of urine collected in the 24 hour period (mL), C_{serum} is the serum creatinine concentration (μmol/L). The volume of urine should be converted to ml/min by dividing the total volume of urine collected over the 24-hour study period by 1440.

Another approach to estimating GFR is using a simplified Levey equation (41), which was developed from the Modification of Diet in Renal Disease (MDRD) study. The Levey or MDRD equation was based on data collected during the clinical trial to assess diet and other factors on the progression of kidney disease. The Levey equation is based on direct measurement of GFR using iothalamate, and the resulting estimation equation incorporates the variables of serum creatinine, age, sex, weight and race. This method was derived from a population of patients with chronic renal disease, which would be expected to be considerably different to the population of critically ill patients treated with CVVHDF, who present with a wider range of disease states.

$GFR = 186 \times (Scr^{-1.54}) \times (Age^{-0.203}) \times (1.21 \text{ if AA})$ .males (Equation 1.5.3.9)

GFR = male value x 0.742..... females (Equation 1.5.3.10)

where AA is African American, GFR= Glomerular filtration rate, Scr = serum creatinine.

Once a GFR is estimated using one of the approaches described, the degree of renal impairment can be classified (as per BNF classifications, Appendix 3)

Classification	GFR (ml/min)
Mild	20-50
Moderate	10-20
Severe	<10

Theoretically, the ideal method of estimating Cl_{cr} should consider all factors that influence creatinine production and an estimate of nonrenal creatinine elimination.

As the method will be ideally applicable to patients with characteristics similar to those from whom the relationships were derived, either broad populations should be studied or the method validated retrospectively for other populations.

The most significant limitation of the methods that use a single serum creatinine measurement is the requirement for a steady-state serum creatinine value (e.g. two values obtained within 24 hours varying by less than 10-15%).

Another limitation of using Cl_{cr} as an indicator of GFR is that 10% of creatinine elimination is a result of tubular secretion in individuals with normal renal function and that the fraction of creatinine eliminated by secretion increases as kidney function declines, therefore Cl_{cr} will overestimate GFR at low levels of kidney function.

The Cl_{cr} of patients, whose renal function is changing, for example patients with acute renal failure, can be estimated using a number of methods. These methods do not require a steady state serum creatinine measurement and so can be used when serum creatinine values are increasing or decreasing. One such method is the Jelliffe and Jelliffe method (42); Clcr is estimated in four steps 1) The urinary creatinine excretion rate is estimated from Equation 1.5.3.11/15 These equations estimate steady-state urinary excretion rate (E^{SS}) from age and body weight. 2) Step 2 corrects E^{SS} for nonrenal creatinine elimination. 3) If Scr is at steady-state, E^{SS}corr is used to estimate Cl_{cr} in Equation 1.5.3.13, but if Scr is changing, the urinary creatinine excretion rate is probably not at steady state, and the current creatinine excretion rate (E) must be estimated. E is related to the current Scr and when Scr is changing, E rather than E^{SS}corr must

be used to estimate Cl_{cr}. According to equation 1.5.3.12, when Scr is not at steady-state, E will differ from E^{SS}corr by an amount equal to the daily accumulation (or loss) of creatinine by the body, where Scr1 is the serum creatinine concentration D days ago, Scr2 is the current serum creatinine concentration and B.W. is body weight in kilograms; when B.W. is multiplied by 4, it is an estimate of Vd of creatinine in decilitres. Substitution of E into equation 1.5.3.14/18 allows calculation of an estimated Clcr.

Males:

E^{SS} = IBW (kg) X (29.3 – 0.203.age (years)) (Equation 1.5.3.11)

E^{SS}corr = E^{SS} x (1.035 -0.0337.(Scr)) (Equation 1.5.3.12)

E= E^{SS}corr – {4 x IBW x (Scr2-Scr1)}/Δt day (Equation 1.5.3.13)

Clcr = E/ 14.4(Scr) (Equation 1.5.3.14)

Females:

E^{SS} = IBW X (25.1 – 0.175.age) (Equation 1.5.3.15)

E^{SS}corr = E^{SS} x (1.035 -0.0337.(Scr)) (Equation 1.5.3.16)

E= E^{SS}corr – {4 x IBW x (Scr2-Scr1)}/Δt day (Equation 1.5.3.17)

Clcr = E/ 14.4(Scr) (Equation 1.5.3.18)

If the serum creatinine is rising, it is likely that it is not at steady-state. Thus, if the rising serum creatinine concentration is used in the Cockcroft and Gault equation, the patient's creatinine clearance will be overestimated. Serum creatinine concentrations may require a duration of one week to stabilise following a decrease in renal function. Conversely, after renal function improves to normal, the shift of serum creatinine concentrations to its new steady-state level occurs rapidly, since the new half life is now quite short. Thus, the probability that serum creatinine may not be at steady-state is much greater when serum creatinine is rising, than when it is falling. Jelliffe's

multistep method, which corrects for rising serum creatinine, is more accurate than the Cockcroft and Gault equation in patients with unstable renal function. When using the Jelliffe and Jelliffe method, the most recent serum creatinine value should be used in place of an average serum creatinine value when it is rising, which will provide a lower estimate of Clcr and a more conservative dosage adjustment in the face of declining renal function.

The method of Chiou et al (43) uses creatinine production as a function of age and sex, an assumed volume of distribution for creatinine that is not changed in patients with renal failure. The percent of total body weight that represents total body water is variable with respect to age, sex and total body weight. Thus, the ideal body weight of an individual patient should be used in this equation.

$Vd = 0.6$ L/kg (IBW) (males/females) (Equation 1.5.3.19)

$Clcr = 2$ IBW x [28-0.2(age)]/14.4 x $[Scr_1 + Scr_2]$+ 2[Vd(Scr_1.Scr_2)]/(Scr1 + Scr2) x (Δtmin) – [Cl_{cr}^{NR} x IBW) (males) (Equation 1.5.3.20)

$Clcr = 2$ IBW x [22.4-0.16(age)]/14.4 x $[Scr_1 + Scr_2]$+ 2[V(Scr_1.Scr_2)]/(S_{cr1} + S_{cr2}) x (Δtmin) – [Cl_{cr}^{NR} x IBW) (females) (Equation 1.5.3.21)

Lott and Hayton (44) have suggested an approach using IBW:

Clcr = (145-age) x weight (LBW)/SrCr x 72 *0.85 (Equation 1.5.3.22)

Hull et al (45) proposed the following relationship:

Clcr = (145-age) -3/SrCr x wt/70 * 0.85 (Equation 1.5.3.23)

Winter (46) suggested the following equation:

$$Clcr = \frac{\text{(Production of creatinine in mg/day)} - [(SCr_2\text{-}SCr_1)(Vcr)/t)\ (10dL/L)]}{(SCr2)(10dL/L)}$$

X 1000mL/L/1440min/day (Equation 1.5.3.24)

Estimation of creatinine clearance from serum creatinine values in dialysed patients with severe renal impairment is difficult and imprecise. This is because the serum creatinine value that has been artificially lowered by dialysis does not reflect the functional capacity of the glomerulus.

1.6. Altered Pharmacokinetics in Patients with Renal Insufficiency

1.6.1 Altered Drug Absorption

Drug absorption may be altered in patients with renal disease as a result of changes in gastric pH and gastric emptying times, for example due to peritonitis or autonomic neuropathy in Diabetes Mellitus. Patients with renal disease are often uraemic, which can result in increased gastric pH, when urea is converted to ammonia. The concomitant administration of drugs to patients with renal disease may also alter the absorption of others. Calcium-containing phosphate binders (calcium carbonate and acetate) may bind with drugs within the gastrointestinal tract, therefore reducing the bioavailability of these agents, by physically adsorbing to the drug or forming insoluble complexes. This has been demonstrated for digoxin, multiple fluoroquinolone antibiotics and a number of other agents (47,48). Additionally, these antacids used as oral phosphate binders can alter systemic absorption by changing gastric pH.

1.6.2. Altered drug distribution

Changes in drug distribution as a result of renal insufficiency may result from fluid retention leading to a change in the Vd of water-soluble drugs or as a result of uraemia and associated changes in the protein binding of drugs in tissue and plasma. V_1 which approximates extracellular fluid volume or blood volume for many drugs may be increased in renal disease, particularly, in patients with oliguric ARF. Protein binding of many acidic drugs is reduced in patients with renal failure, for example, penicillins, cephalosporins,

theophylline and phenytoin (49, 50). Possible explanations for this include hypoalbuminaemia (resulting from uraemia or nephrotic syndrome), competition for binding sites by accumulated endogenous (uremic) substances or other drugs or metabolites.

1.6.3 Altered Drug Metabolism

Various studies have shown that renal failure may affect the clearance of a drug even if its primary route of elimination is not urinary excretion. A relationship between reduced hepatic enzymatic activity and renal insufficiency has been suggested by Patterson et al (51). A number of investigators (51-53) have demonstrated altered drug disposition in patients with chronic renal insufficiency on the basis of reduced hepatic as well as renal clearance. It appears that although the elimination of the parent compound may be unchanged, the formation of metabolites may be altered, thus affecting the overall rate and extent of excretion of the drug. In contrast, there have been reports of higher residual nonrenal clearance of some drugs in critically ill patients with acute renal failure. These conflicting reports in patients with chronic versus acute renal failure may be due to less exposure to or accumulation of uremic waste products with acute renal failure, which potentially alter hepatic function. In patients with chronic renal impairment, administration of long-term drug therapy may result in the accumulation of drug metabolites that are primarily renally eliminated. If an accumulated metabolite is pharmacologically active, then there is an increased risk of prolonged duration of drug effect and toxicity. An example of this phenomenon is the accumulation of the morphine metabolite, morphine-6-glucuronide, in patients with renal insufficiency, resulting in symptoms of morphine toxicity. Although renal excretion of unchanged morphine is low (3-7% of its total

elimination), its metabolite, morphine-6-glucuronide, is eliminated by the kidneys. It is pharmacologically active, has been shown to cross the blood-brain barrier, has a greater affinity for brain tissue than the parent drug and has a more prolonged duration of action than morphine (54).

The kidney contains many of the metabolic enzymes that are also found in the liver, such as cytochrome P450, but the contribution of the kidneys to total metabolic activity is comparatively low. The effect of renal insufficiency on renal drug metabolism means that patients with renal impairment require administration of vitamin D in the form of 1α-hydoxycholecalciferol or 1,25-dihydroxycholecalciferol in order to increase the absorption of calcium and prevent renal bone disease. This is because metabolic activation of vitamin D, obtained from diet or synthesised in the skin, requires hydroxylation at both the 25 position in the liver and the 1α-position in the kidney. The kidneys are also the major site of production of erythropoietin. Patients with severe renal disease develop a profound anaemia which is treated with iv or sc injections of human recombinant erythropoietin.

1.6.4 Altered Drug Excretion

The rate of excretion of substances by the kidney is equal to the rate of filtration plus the rate of secretion minus the rate of reabsorption. The clearance of a drug as a result of glomerular filtration is dependent on the patient's Glomerular Filtration Rate (GFR) and the fraction of the drug not bound to plasma proteins. Active tubular secretion of a drug in the proximal tubule may be via the anionic or cationic substrate-specific pathway, depending on the affinity of the tubular transport sites for the drug molecule, the capacity of the site to actively transport the molecules into the lumen, and renal blood flow. The passive tubular reabsorption of a drug is determined by its degree of

lipophilicity, degree of ionisation (pKa and pH) and the urine flow rate. Reabsorption must occur if the Cl_R is less than Cl_{GFR}. Highly lipid-soluble drugs may be completely reabsorbed. The relative contribution of each of these processes to the renal excretion of any particular drug may vary greatly.

Many diseases that affect the kidney preferentially alter the normal histology of the glomeruli or tubules. However, according to the intact nephron hypothesis the function of all segments of the remaining nephron are affected equally. Thus, regardless of whether a drug is excreted primarily by glomerular filtration or active tubular excretion, the assumption is that its renal clearance is reduced in proportion to the reduction in creatinine clearance or glomerular filtration rate.

1.6.5 Modification of drug dosing in renal insufficiency

Progressive reductions in renal clearance and clearance of a drug that is primarily renally eliminated would be anticipated with decreasing renal function. For drugs that rely on the kidney for elimination (>30%), drug dose adjustment is generally recommended. In general, dose modification is carried out on the basis that a reduction in GFR and Cl_{cr} is proportional to a concomitant reduction in drug clearance. While this is applicable for most patients, in particular patients with rapidly changing renal status (for example, ARF), with different aetiologies of renal disease and certain co-morbidities, this may not be true. At present, for new drug entities, drug companies provide data on the fraction of unchanged drug renally eliminated and an assessment of the relationship between renal function and the drug's pharmacokinetic parameters. However, reports of drug disposition in various degrees of renal insufficiency published by drug companies are based on small number of

patients with a narrow spectrum of renal disease and so care must be taken when extrapolating these results to an individual patient.

In order to avoid accumulation of drugs primarily eliminated by the kidneys during renal insufficiency, two main approaches may be adopted; either

1) The dose must be decreased or

2) The dosage interval must be increased.

The underlying pharmacokinetic model is:

Maintenance Dose = Cpss * Cl. (Equation 1.6.4.1)

Thus estimation of the drug's renal clearance is based on creatinine clearance. Tozer and Welling et al (55,56)developed methods for predicting the elimination rate constant or Cl of a patient with renal insufficiency from the fraction of drug eliminated renally unchanged in subjects with normal renal function (fe) and the ratio (KF) of the patients creatinine clearance to a presumed normal creatinine clearance of 120ml/min x 1.73 m^{-2}.

Specific equations for 22 drugs were derived by Welling et al (55), while Tozer et al (56) proposed the following general equations:

$k_e^{REN} = k_e^{NORM} \times Q$ (Equation 1.6.4.2)

$Cl^{REN} = Cl^{NORM} \times Q$ (Equation 1.6.4.3)

Where $Q = 1-\{fe(1-KF)\}$ (Equation 1.6.4.4)

where k_e^{REN} = elimination rate constant of a patient with renal insufficiency,

k_e^{NORM} =elimination rate constant of a patient with normal renal function

Q = dosage adjustment factor

fe = fraction of drug eliminated renally unchanged in subjects with normal renal function

KF = ratio of the patient's Clcr to a presumed normal Clcr of 120ml/min-1 x1.73m-2.

Thus, a stepwise approach to drug dosing during renal impairment could be as follows:

1. Calculate dose adjustment factor: Q

If limited pharmacokinetic data is available for the drug:

$Q = 1-\{fe(1-KF)\}$ (Equation 1.6.4.5)

$KF = Clcr_{(REN)}/Clcr_{(N)}$ (Equation 1.6.4.6)

If extensive pharmacokinetic data is available:

$Q = Cl_{REN}/Cl_N$ (Equation 1.6.4.7)

2. Calculate new dose input rate

Once the dosage adjustment factor has been estimated, the dosage regimen can be modified on the basis of the desired serum concentration profile. If there is a significant therapeutic relationship between Cpmax or Cpmin concentrations and efficacy or toxicity, then the dosage regimen should be designed to achieve and maintain these target concentrations. However, if there is no specific desired peak or trough concentration or no specified therapeutic concentration range, then the goal of the modified dosage regimen should be to attain the same mean steady-state concentration (C_{pss}) that has been associated with therapeutic efficacy in patients with normal renal function.

If a drug is administered by continuous intravenous infusion, with an infusion rate k_0, and the desired goal is to maintain a specified C_{pss}, the adjusted dosage regimen can be calculated as:

$k_0^{REN} = k_0^{NORM} \times Q.$ (Equation 1.6.4.8)

If no loading dose is administered, it will take four to five half-lives for the desired Cp_{ss} to be achieved and a loading dose can be calculated as follows and can be administered to achieve therapeutic concentrations more rapidly:

Loading Dose $= C_{SS}. V^{REN}. TBW.$ (Equation 1.6.4.9)

When a drug is administered intermittently, the dosage adjustment will depend on the desired goal. If the primary goal is to maintain the Cpss, then either the dose can be reduced or the dosage interval extended.

$$D_{REN} = D_n * Q \qquad \text{(Equation 1.6.4.10)}$$

$$T_{REN} = T_n / Q \qquad \text{(Equation 1.6.4.11)}$$

Both of these adjustment methods will achieve the same C_{ssave}, but the resultant steady-state peak and trough concentrations will differ significantly. The reduced dose method results in a lower peak concentration and higher trough and the prolonged interval method should result in concentrations similar to those in patients with normal renal function. This may have implications with regard to efficacy or toxicity, depending on the pharmacodynamics and toxicity profile of the drug. In practice, modification of both the dose and the dosage interval may be necessary.

This general approach to designing a dosage regimen for a patient with renal insufficiency is based on a number of assumptions (56):

1. the elimination of the drug can be described by a first-order one-compartment model
2. glomerular and tubular function decrease to the same extent in all renal diseases
3. the bioavailability, protein binding, volume of distribution and non-renal clearance of the drug are not altered by renal insufficiency
4. the concentration-effect relationship of the drug is not changed.
5. the metabolites of the drug are pharmacologically inactive and do not accumulate in the presence of renal insufficiency.

These methods of dosage individualisation are predominantly employed in the clinical setting when there is no drug serum concentration data available to

guide dosing regimen design. These approaches to drug dosing in renal impairment have been evaluated for a number of drugs and are an improvement on empiric therapy. However, they are still associated with error and the monitoring of serum drug concentrations in individual patients is a more accurate way of attaining a target serum concentration-time profile in an individual patient with renal impairment. Drugs with a low therapeutic index and significant renal clearance, such as aminoglycosides, vancomycin, digoxin and lithium, all necessitate serum concentration monitoring in patients with renal impairment and the elderly.

1.7 Therapeutic Drug Monitoring

1.7.1 Definition

Therapeutic Drug Monitoring (TDM) can be defined as the use of plasma drug concentrations, pharmacokinetic principles and pharmacodynamic factors to optimise drug therapy in an individual patient. There are two main reasons for monitoring drug concentrations in plasma/serum in the clinical setting:

1) To determine whether a therapeutic or toxic concentration has been produced by a given dosage regimen.
2) To estimate pharmacokinetic parameters of a drug for the purpose of dose individualisation.

Therapeutic drug monitoring is appropriate for drugs where the intensity of the pharmacological effect or therapeutic efficacy is proportional to the drug concentration in plasma. Within the optimum therapeutic concentration range, the drug exhibits maximum efficacy and minimum toxicity in the majority of patients. However, the therapeutic range should not be considered in absolute terms. Interpretation of the therapeutic range must consider the disease state for which the drug is prescribed, the age of the patient, concurrent medication,

inheritance and any factors that will alter the drug's volume of distribution or protein binding.

The goal of TDM is optimisation of drug therapy for individual patients. This may involve minimising the probability of toxicity or increasing the probability of the desired therapeutic effect. Drugs that frequently produce toxicity at dosages close to those required for therapeutic effects are most frequently monitored and are the drugs for which commercial assays are usually available. With these drugs, the target serum concentration range is usually narrow, requiring optimal selection of drug dosage and dosing interval. Conversely for drugs with a wide therapeutic index, high enough doses to yield a high probability of therapeutic efficacy may be administered with little risk of toxicity and for these drugs; plasma concentration monitoring is rarely undertaken.

Drugs whose concentrations are routinely monitored in the clinical setting tend to exhibit the following characteristics;

1. Narrow therapeutic index
2. Well–defined relationship between the drug's serum concentrations and clinical effect (therapeutic or toxic effects)
3. Wide interpatient variability in drug handling (pharmacokinetic parameters)
4. Poor correlation between dose and effect
5. A toxicity profile that is difficult to detect clinically

1.7.2 Factors affecting interpretation of Drug Concentration Data

There are numerous drug, patient, logistical and analytical variables that influence the interpretation of drug concentration data.

The interpretation of serum drug concentration data requires knowledge of the patient's physical details, clinical and biochemical status. The patient's drug history, concurrent medications and the patient's disease and biological tolerance to drug therapy must be considered. The most recent drug dosing history; the time, the route and dose of drug given must be recorded. In order to interpret drug concentrations, it is essential to know exactly when the sample was obtained in relation to the last dose administered and when the dosage regimen was initiated. Other issues for consideration include handling and storage conditions of samples, precision and accuracy of the analytical method, validity of pharmacokinetic models and assumptions.

Based on knowledge of these factors, the patient's individual pharmacokinetic parameters can be estimated. One approach is to use an iterative technique whereby population pharmacokinetic data is used to calculate a set of initial pharmacokinetic parameters and a level is predicted for the time the blood sample was taken. This value is compared to the assay result and the elimination rate constant is changed stepwise by iteration until the predicted level approximates the measured level. This technique can only be used if the Vd of the drug does not vary widely. The new clearance is estimated from the product of the Vd and k, and this can be compared with the population clearance. If the patient's parameters vary widely from the population parameters, reasons for this deviation include: altered pharmacokinetic parameters due to a disease state or organ impairment, drug interactions, non-compliance, medication error, incorrect assay result, timing of sampling, site of sampling, storage of samples.

1.8. Renal Replacement Therapy

1.8.1 Principles of RRT

Resolution of severe acute renal failure can take several days or weeks. During this period, the kidneys cannot maintain homeostasis of fluid, potassium, metabolic acid and waste products. Life-threatening complications inevitably develop in such patients. Extracorporeal techniques of blood purification must therefore be applied to prevent such complications. Indications for Renal Replacement Therapy (RRT) include acidosis or electrolyte disturbances that do not respond to pharmacologic therapy, fluid overload that does not respond to diuretics, and uraemia. Renal replacement therapy techniques include haemodiafiltration, haemofiltration, intermittent haemodialysis and peritoneal dialysis. All of these techniques rely on the principle of removing unwanted solutes and water through a semipermeable membrane, which is either artificial (haemodialysis or haemofiltration membranes) or biological (peritoneum). During Renal Replacement Therapy (RRT), water is removed through a process called ultrafiltration. It requires a driving force to move across a semipermeable membrance because such fluid would normally be kept within the circulation due to oncotic pressure. This pressure is achieved by either generating a transmembrane pressure as in the case of haemofiltration or haemodialysis that is greater than oncotic pressure or by increasing the osmolarity of the dialysate as in peritoneal dialysis.

Solutes that can pass through the membrane pores are transported by two different mechanisms: diffusion and ultrafiltration (convection). Solute removal can be achieved by creating an electro chemical gradient across the membrane by using a flow past system with toxin-free dialysate (diffusion), as in intermittent haemodialysis (IHD) and peritoneal dialysis (PD). Alternatively,

a 'solvent drag' can be created that is driven by transmembrane pressure, where solute moves together with solvent (convection) across a porous membrane where it is discarded and then replaced with toxin-free replacement fluid as in haemofiltration.

1.8.2 Mechanisms of solute removal during RRT

Solute removal by haemodialysis is due to diffusion. The rate of diffusion of a given solute depends on its molecular weight, the porosity of the membrane, the blood flow rate, the dialysate flow rate, its binding to proteins and its concentration gradient across the membrane.

- Concentration gradient – the relative rates of passage of a given solute from solution A to solution B will depend on the frequency of collisions of solute molecules with each side of the membrane, which will depend in turn on the relative concentrations of the solute on each side of the membrane. The net rate of transfer of a given solute form solution A to solution B will be greatest when the concentration gradient between the two solutions for that particular solute is highest.
- Molecular weight – the larger the molecular weight of a solute, the slower will be its rate of transport across a semipermeable membrane. This relates to speed and size. The velocity of a molecule in solution is inversely related to the molecular weight of the molecule. Small molecules, moving about at high velocity will collide with the membrane often, and their rate of diffusion transport through the membrane will be high. Large molecules, even when they can fit easily through the membrane pores, will diffuse through the membrane slowly because they will be moving along at low velocity and colliding with the membranes infrequently. The molecular weight of a solute

correlates highly with its size. The membrane will partially or completely inhibit passage of a solute as its molecular size approaches and exceeds the size of the membrane pores.

- Membrane resistance – the resistance of the membrane to solute transport will be high if the membrane is thick, if the number of pores is small or the pores are narrow. Unstirred layers of fluid on either side of the membrane inhibit diffusion because they act to decrease the 'effective' concentration gradient at the membrane surface. The thickness of these unstirred layers is affected by dialysis solution and blood flow rates and by dialyser design.

The second mechanism of solute transport across semipermeable membranes is ultrafiltration (convective transport). This is the primary mechanism of solute removal during haemofiltration. Water molecules are extremely small and can pass through all semi-permeable membranes. Ultrafiltration occurs when water driven by either a hydrostatic or an osmotic force is pushed the membrane. Those solutes that can pass easily through the membrane pores are swept along with the water ('solvent drag'). The water being pushed through the membrane is accompanied by such solutes at close to their original concentrations. Larger solutes, especially those that are larger than the membrane pores are held back. For such large solutes, the membrane acts as a sieve. Hydrostatic ultrafiltration depends on transmembrane pressure and the permeability of the membrane to water. During haemofiltration, water (along with small solutes) moves from the blood to dialysate in the dialyser as a result of a hydrostatic pressure gradient between the blood and dialysate compartments. The rate of ultrafiltration will depend on the total pressure difference across the membrane (calculated as the pressure in the blood compartment minus the pressure in the dialysate

compartment).The permeability of dialyser membranes to water, though high, can vary considerably and is a function of membrane thickness and pore size. Ultrafiltration has significant implications for solute clearance in haemofiltration and haemodiafiltration. Whereas diffusive removal of a solute depends on its size, all ultrafiltered solutes below the membrane pore size are removed at approximately the same rate. This principle is the basis for coupling the infusion of a replacement fluid with a large amount of ultrafiltation (more than is required to establish euvolemia). Although haemodialysis and haemofiltration often have comparable removal of small solutes such as urea (MW=60), haemofiltration can produce much higher removal of larger, poorly diffusible solutes such as inulin (MW = 5200) (58, 59).

1.8.3 Type of membrane

The membranes used in the extracorporeal circuit can differ in both the material used and their configuration. The materials used include (1) Synthetics, (2) Cellulose, (3) Cellulose esters. Synthetic membranes are generally preferred due to the higher clearances achieved and their improved biocompatibility properties. Copolymers such as polyacryonitrile, polyamide or polysulfone are used to manufacture these membranes. Kronfol et al (60) investigated the effect of Continuous Arterioveonous Haemofiltration (CAVH) membrane types (polysulfone, polyacrylonitrile, polyamide and polysulfone) on drug-sieving coefficients and clearances. The drugs investigated were valproic acid, theophylline, phenytoin, tobramycin, digoxin and vancomycin. Digoxin exhibited a different sieving coefficient for each filter studied and there was variability between at least two filters for each drug. The investigators concluded that the various types of filters have different sieving

coefficients and that each drug must be studied individually to determine its sieving coefficient and expected clearance. Philips et al (61) investigated an in-vitro model of cefpirome clearance using three membrane types at varying ultrafiltrate and dialysate flow rates. They found that during haemofiltration cefpirome crossed hollow fibre polyamide (PA) and polyacrylonitrile (PAN) membranes with equal efficiency. Using a haemodiafiltration model in the same study (61), cefpirome was found to penetrate PAN membranes (flat plate AN69S) more efficiently than hollow fiber PA membranes (FH66D). Schaeffer et al measured the filter performance of six polyamide haemofilters with a running time exceeding 72 hours applied for continuous haemofiltration in intensive care patients. They found that the sieving coefficients of polyfructosan, urea and creatinine did not change with running time within the first 72 hours of treatment. Dungen et al (62) found that a filter with long hollow fibers had a better performance than a filter with more and shorter hollow fibers. Joy et al (63) performed controlled clearance studies in five stable haemodialysis patients with three filters; an acrylonitrile copolymer (AN69), polymethylmethacrylate (PMMA) and polysulfone membrane. The clearance of vancomycin was essentially constant for all three filters, suggesting that clearance of vancomycin was not membrane dependent during CVVH (63).

1.9 Continuous Renal Replacement Therapy (CRRT)

The popularity of slow continuous therapies for the treatment of critically ill patients with renal failure is increasing. Initially, CRRT was first performed as an arteriovenous therapy (Continuous Arteriovenous Haemofiltration, CAVH), where blood flow through the haemofilter was driven by the patient's blood pressure. However, clearances were low and countercurrent dialysate flow was

soon added to double or triple solute clearances, with or without spontaneous ultrafiltration, and so continuous arteriovenous haemodialysis/diafiltration (CAVHD/CAVHDF) were developed. In order to avoid the need to cannulate an artery, double-lumen catheters and peristaltic blood pumps have come into use, with or without the control of ultrafiltration rates (Continuous Venovenous Haemofiltration). In a veno-venous sytem, dialysate can also be delivered countercurrent to blood flow (Continuous Venovenous Haemodialysis/Haemodiafiltration) to achieve either almost pure diffusive clearance or a mixture of diffusive and convective clearance.

Benefits of CRRT, irrespective of the technique used, include:

- Continuous control of fluid status – highly effective in removing fluid (postsurgery, pulmonary oedema, acute respiratory distress syndrome)
- Haemodynamic stability – haemodynamically well tolerated with minimal change in plasma osmolality
- Control of azotemia and electrolyte and acid-base balance, corrects abnormalities as they arise.
- Facilitates administration of (protein rich) parenteral nutrition and essential intravenous medications, while achieving uraemic control
- Minimal risk of infection
- High level of biocompatibility.

1.9.1 Factors affecting drug clearance by CRRT

Because of the pore size of the dialysis membranes, only substances not bound to plasma proteins will pass through the membrane either by diffusion or filtration. The free unbound fraction that may be freely filtered through the membrane is calculated as (64):

Free fraction = (1- Protein bound fraction) (Equation 1.9.1.1)

If hemofiltration is performed in the postdilution mode, the ultrafiltrate generated by the procedure contains all drug that is not protein bound in the same concentration as in the plasma entering the dialyzer through the arterial line. Clearance of a non-protein bound drug equals the ultrafiltration (UF) rate in postdilutional haemofiltration. For protein bound drugs the ultrafiltration rate has to be multiplied by the free fraction:

Drug clearance (ml/min) = UF rate (ml/min) x (1- protein bound fraction) (Equation 1.9.1.2)

If haemofiltration is used in the predilution mode, the patient's blood is diluted with a substitute fluid prior to entry into the dialyser. Therefore the drug concentration in the plasma entering the dialyser is lower than the plasma drug concentrations in the patient's circulation. The ultrafiltrate contains the non-protein bound drug in the same concentration as in the plasma water of the blood inside the dialyser, but this is lower than in the patient's blood. This predilutional effect can be calculated from blood flow / (blood flow + substitution rate), and the correction must be integrated in the clearance (65):

Drug clearance$_{\text{predilution HF}}$ (ml/min) = UF rate x (1- protein bound fraction) x blood flow rate / (blood flow rate + substitution rate) (Equation 1.9.1.3)

Drug clearance in haemodialysis depends on the molecular weight of the drug, for example, vancomycin, a middle-molecular weight drug is poorly cleared by haemodialysis. Drug adsorption to the haemodialysis membrane is another consideration. The rate of drug clearance can increase over time, when the initial drug adsorption to the membrane is complete – this has been reported for gentamicin (66) and tobramycin (67). Competition of elimination pathways is critical in evaluating the clinical relevance of CRRT clearance. If a drug is primarily hepatically cleared, such as metronidazole, its clearance by CRRT is

less significant than for a drug which is primarily renally excreted. As the non-renal clearance of vancomycin is so low (5ml/min), a CRRT clearance, of 15ml/min, would increase the total vancomycin clearance fourfold, and a correspondingly higher dose would be required.

1.9.2 Adjustment of Drug Dose during CRRT

Drug clearance by CRRT only appears to be clinically relevant when it exceeds 25% of the total body clearance of the drug. If CRRT clearance is clinically significant, then dosage adjustment may be required. A number of different approaches can be used to estimate a suitable maintenance dose for a patient receiving CRRT. One simple method is to choose a dose based on an estimate of the clearance of creatinine due to the CRRT system. For haemofiltration systems, the ultrafiltration rate and for haemodialysis sytems, the dialysis flow rate can be used to represent the creatinine clearance. Then, for example, an ultrafiltration rate of 2L/hr can be interpreted as being equivalent to a creatinine clearance of 33.3ml/min and so the dose selected would be the dose usually administered to a patient with moderate renal failure (68). This approach assumes that creatinine is removed freely and completely by the filter (sieving coefficient of 1). The sieving coefficient, the ratio of drug concentration in the effluent fluid (ultrafiltrate/dialysate) to that in serum, is a measure of the permeability of the haemofilter to a specific compound. A second approach to estimating a suitable maintenance dose during CRRT is to use the sieving coefficient of the drug to estimate the drug clearance due to CRRT. The sieving coefficient of a drug is dependent on its physiochemical properties and should be similar to the non-protein-bound fraction. A drug that passes freely through the filter will have a sieving coefficient (SC) of 1 and a drug that is not removed at all will have a SC of 0. Several investigators (69,

70, 71) have proposed the following equation for estimating SC in the clinical setting this expression can be simplified as follows:

$SC = C_{eff}/C_a$ (Equation 1.9.2.1)

Where C_{eff} is the concentration in the effluent fluid (ultrafiltrate/dialysate) and C_a is the concentration of the drug in the arterial circulation or the pre-filter concentration. The SC is often approximated by the fraction unbound of the drug (fu) because this information may be more readily available. Thus, the clearance by CVVH can be calculated as

$Cl_{CVVH} = UFR \times SC$ (Equation 1.9.2.2)

Or

$Cl_{CVVH} = UFR \times fu$ (Equation 1.9.2.3)

Sieving coefficient values are unique to the filter system used to generate the value (60). System variables that will affect drug clearance include ultrafiltration and dialysis fluid rates, the type of membrane used, the blood flow rate, differences in actual flow rates achieved over time and patient factors such as coagulopathy. In CVVHDF, drug clearance occurs through combined diffusive and convective forces and so both the ultrafiltration rates and dialysis rates achieved will influence the sieving coefficient. The use of data extrapolated from studies involving dialysis or ultrafiltration alone will not always be appropriate for guiding dosing during CVVHDF. Clearance of a drug by CVVHDF is generally greater than by CVVH. The Cl_{CVVHF} can be approximated from the equation:

$Cl_{CVVHDF} = (UFR + DFR) \times (fu \text{ or } SC)$ (Equation 1.9.2.4)

In the clinical setting, it is not possible to separate these two components (convective, diffusive) of Cl_{CVVHDF}. In essence, the Cl_{CVVHDF} is calculated as the product of the combined ultrafiltrate and dialysate volume (V_{eff}) and the

concentration of the drug in this effluent fluid (C_{eff}) divided by the serum concentration (C_{mid}) at the midpoint of the V_{eff} collection period.

Depending on the drug, it may be more appropriate to shorten the dosing interval or to increase the dose. For a renally eliminated drug, the extracorporeal clearance (calculated using the sieving coefficient and the ultrafiltrate/dialysate rates) can be used to determine the maintenance dose required using the equation, described by Reetze-Bonorderen et al (72).

$$MD = D_{anuric} \times (1/1-f_{RRT}) \qquad \text{(Equation 1.9.2.5)}$$

Where D_{anuric} is recommended dose for anuric patients, f_{RRT} is the fraction of drug eliminated by the extracorporeal route = Cl_{RRT} / TBC.

Various approaches to dosage adjustment during CRRT have been suggested in the literature using the following pharmacokinetic parameters.

- Clearance in anuric non-dialysed patients = non-renal clearance
- Half-life of the drug in anuric non-dialysed patients
- Dosing interval in anuric non-dialysed patients
- Dose in anuric non-dialysed patients
- Protein binding to estimate drug CRRT clearance

Using the clearance value in an anuric non-dialysed patient, to estimate the non-renal drug clearance and factoring in the clearance due to CRRT, the dosage interval used in anuric, non-dialysed patients can be corrected to reflect the CRRT clearance;

$$Interval_{CRRT} = Interval_{anuria} [Clearance_{anuria} / Clearance_{anuria} + Clearance_{CRRT}] \qquad \text{(Equation 1.9.2.6)}$$

Similarly, the dose used in anuric, non-dialysed patients can be increased to account for the shorter half-life and increased drug clearance during CRRT therapy.

$$Dose_{CRRT} = Dose_{anuria} \left[1 + \{ (Cl_{CRRT} / Cl_{anuria}) / 2^{Interval / halflife} \} \right]$$

(Equation 1.9.2.7)

According to Dettli's fundamental equation, drug clearance (Cl) is a linear function of Cl_{cr} (73). Non-renal drug clearances in healthy volunteers can even be used to predict drug clearance for functionally anuric patients ($Cl_{nonren} = Cl_{anur}$) (73):

$$Cl = Cl_{anur} + a. C_{cr}$$ (Equation 1.9.2.8)

This dependence has been investigated in patients and confirmed for many drugs. Thus the following holds; $a = (Cl_{norm} - Cl_{anur}) / C_{crnorm}$.

The Dettli equation can be applied to haemofiltration circumstances (73) by introducing the total Cl_{cr} concept (Cr_{tot}). Although for continuous haemofiltration, renal C_{cr} (Cr_{ren}) combined with the extracorporeal Cl_{cr} (Cr_{RRT}) yields the total C_{cr} ($Ccr_{tot} = Cren + Ccr_{RRT}$). (Equation 1.9.2.9)

Cr tot = (CrFiltrate. VolumeFiltrate) + (CrUrine. VolumeUrine) / Srcr. 1440

(Equation 1.9.2.10)

1.10 Clinical Studies

There are widely varying data reported in the literature on drug disposition during critical illness extrapolated from non-critically ill patients with renal failure and from critically ill patients without renal failure. The literature on drug pharmacokinetics in critically ill patients becomes more confusing when renal replacement is considered, in part due to the many methods of therapy used. Continuous venovenous haemodiafiltration (CVVHDF) is frequently used as an alternative to conventional haemodialysis in critically ill patients with acute renal failure. However, data on drug clearance during CVVHDF remains relatively scarce. Studies of drug pharmacokinetics during CRRT often describe drug clearances during the oldest and least effective procedures (e.g.

CAVH). Variations in CRRT conditions, such as selection of a different membrane or differences in ultrafiltration rates, must be considered when interpreting results of existing pharmacokinetic studies.

When data from published studies are used to design a dosage regimen; system, patient and drug factors likely to affect drug clearance must be considered. For example, patient factors may include physiological and pathological factors that may result in an altered Vd or non-renal clearance. Drug factors, including molecular weight, protein binding and elimination pathways, will result in variability in drug disposition during CVVHDF. System factors include the rate of ultra filtration and the sieving coefficient of the membrane for haemofiltration. Membrane choice can affect drug clearance; certain membranes may adsorb particular drugs and pore size will affect the clearance of some drugs. Data regarding the clearance of drugs by conventional haemodialysis cannot be accurately extrapolated to CVVHDF because of differences in the membranes used; differences in blood, ultrafiltrate, and dialysate flow rates; and the continuous nature of CVVHDF compared to the intermittent nature of haemodialysis. At the outset of this study, where there was an absence of data on clearance during CVVHDF for a particular drug (e.g. an aminoglycoside), patients were dosed on the basis of their renal impairment. However, there is evidence that drug pharmacokinetics, particularly elimination, may be altered during CVVHDF, resulting in subtherapeutic doses and ineffective therapy. Thus, the progress to therapies with greater clearances and the wider application of these techniques necessitates the reassessment of the impact of CRRT on drug pharmacokinetics.

This project sought to address this requirement by establishing which drugs most warrant investigation and through the subsequent pharmacokinetic evaluation of such drugs during CVVHDF and critical illness. Initially, an audit was carried out to investigate drug prescribing and pharmacokinetic considerations for critically ill patients receiving CRRT. The results of this audit were used to select drugs for pharmacokinetic analysis. Both retrospective and prospective pharmacokinetic studies were designed for this purpose.

1.11 Objectives:

1. To undertake an audit of CVVHDF use during critical illness in the Adelaide and Meath Hospital, Dublin, Incorporating the National Children's' Hospital and to investigate drug use and prescribing practice during CVVHDF.
    - To assess drug prescribing and the use of CVVHDF during critical illness.
    - To investigate the potential impact of CVVHDF on drug pharmacokinetics.
    - To identify drugs requiring pharmacokinetic analysis in critically ill patients receiving CVVHDF.
2. To develop a retrospective method of investigating drug pharmacokinetics during CVVHDF (Continuous Venovenous Haemodiafiltration) for a number of drugs with narrow therapeutic concentration ranges that are commonly used during CVVHDF.
    - To use routinely collected therapeutic drug monitoring data (serum drug concentrations) to calculate pharmacokinetic parameters for

vancomycin, amikacin and gentamicin in critically ill patients undergoing CVVHDF.

- To compare these parameters with literature values for patients with normal renal function and with renally impaired (anephric/acute renal failure) patients not receiving CVVHDF therapy.
- To use these parameters to develop dosing recommendations
- To compare pharmacokinetic parameters calculated retrospectively with reported values from literature prospective studies and ultimately from our own prospective study.

3. To design prospective pharmacokinetic studies for a number of selected drugs (amikacin, gentamicin, ciprofloxacin and vancomycin) in critically ill patients undergoing CVVHDF.
   - To identify the required biological samples and optimal sampling strategy for the pharmacokinetic studies.
   - To develop clinical protocols detailing recruitment and consent procedures, the nature of samples required, sampling times, collection and storage of samples and documentation management.
   - To develop analytical methodologies for ciprofloxacin extraction from biological fluid and for measuring ciprofloxacin concentrations using high performance liquid chromatography.
   - To use serum drug concentration data and effluent fluid concentration data to obtain estimates of drug pharmacokinetic parameters and clearance by the filter during CVVHDF therapy.
   - To identify strategies for dosage adjustment during CVVHDF therapy.

Chapter 2: Materials and Methods

2.1. Clinical Audit of Drug Use and Prescribing Practice during Continuous Venovenous Haemodiafiltration (CVVHDF).

2.1.1 Audit Objectives

1. To describe qualitatively and quantitatively drug prescribing for critically ill patients receiving Continuous Venovenous Haemodiafiltation in the Adelaide and Meath Hospital, Dublin, Incorporating the National Children's Hospital.
2. To evaluate drug prescribing and dosing patterns and to identify which drugs are most commonly prescribed and those which would merit further pharmacokinetic analysis in this population.
3. To examine the evidence-base for existing dosing schedules and to investigate the need for dosage optimisation during CVVHDF.

This audit sought to assess current drug use during CVVHDF and to investigate the evidence-base for current prescribing practice for critically ill patients during CVVHDF. This data was then used as a basis for identifying drugs, whose efficacy is crucial in terms of positive patient outcomes during CVVHDF, but where existing prescribing practice was not adequately underpinned by research.

2.1.2 Study Design

A retrospective audit of drug kardexes, medical charts and computerised reports of microbiologic studies generated during the time period January 2003 - December 2003 was undertaken.

2.1.3 Population

Critically ill patients receiving Continuous Venovenous Haemodiafiltration

2.1.4 Study Sample

The Study Sample included all critically ill patients who received Continuous Venovenous Haemodiafiltration in the Adelaide and Meath, Hospital, Incorporating the National Childrens' Hospital during the time period January-December 20003.

2.1.5 Setting

Medical–Surgical Intensive Care Unit.

2.1.6 Data Collection

All critically ill patients who had received CVVHDF in the hospital in the time period January-December 2003 were included in the study. CVVHDF therapy is only administered in the Intensive Care Unit and when a patient receives CVVHDF, it is recorded in a designated database. This database was used to identify the relevant patients for analysis. After obtaining Hospital Ethics Board approval (Joint Hospitals (AMCNH/SJH) Ethics Board Committee), a retrospective audit of patient drug kardexes and medical charts, generated during the period January-December 2003, was carried out. Computerised reports of microbiological studies and clinical chemistry data created during this time period were also analysed.

2.1.7 Variable Measurement and Definition

A Data Collection Form was developed for recording relevant data from the patients' medical charts and drug kardexes. Patient related variables included a unique identifying number, date of birth, date of starting CVVHDF therapy, date of stopping CVVHDF therapy, number of drugs consumed prior to and during CVVHDF, number of antimicrobial drugs prescribed prior to and during CVVHDF. The date of birth variable was collapsed to age in years for analysis

purposes. Dates of starting and stopping CVVHDF were used to calculate duration of CVVHDF therapy in days.

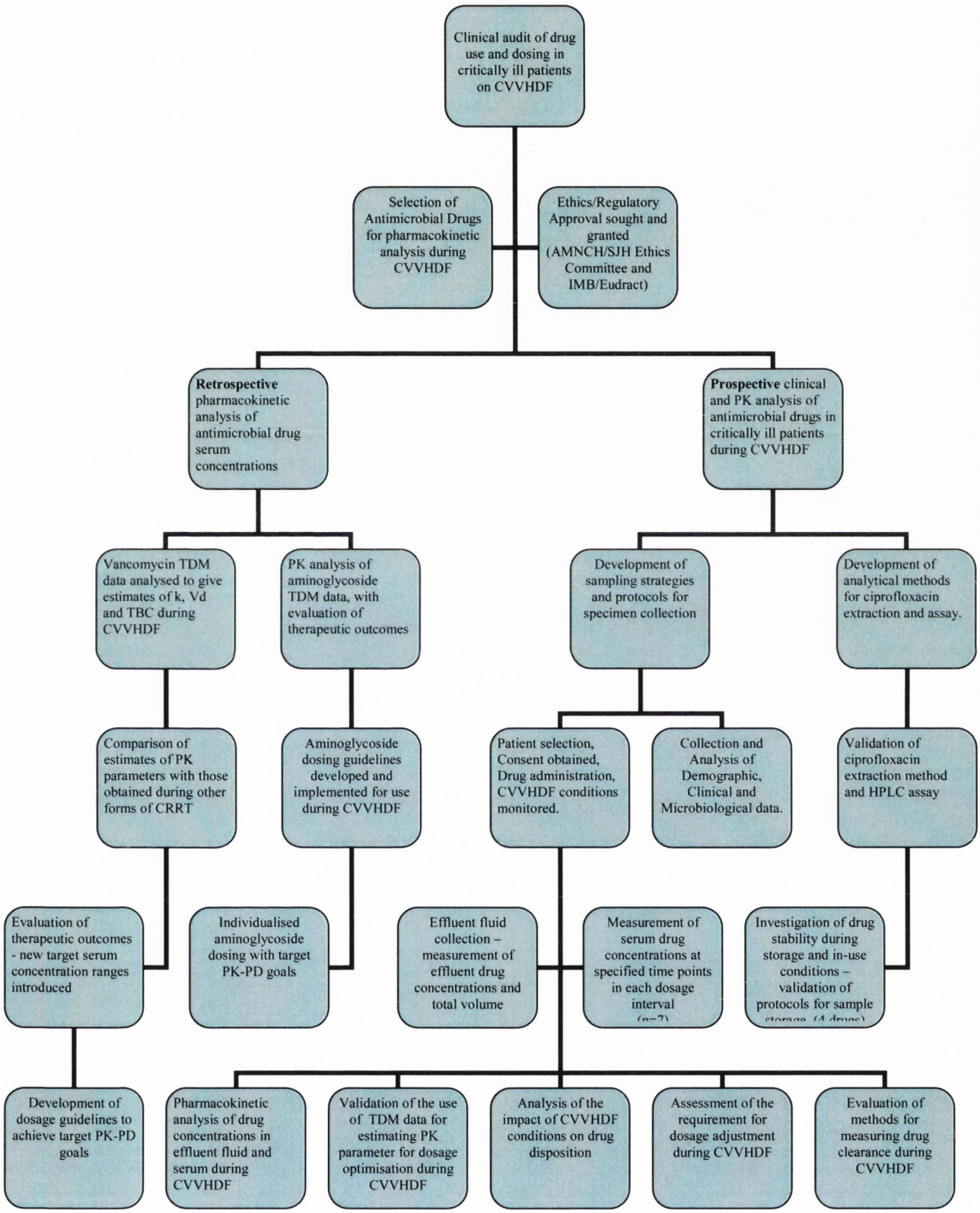
Demographic data such as gender and lifestyle factors were recorded. Gender and obesity were assigned simple binary codes (1/0). Coding for smoking and alcohol was extended to reflect ordinal data collected, with more than two categories for each variable, e.g. smoker, ex-smoker, non-smoker and current alcohol abuse, history of alcohol abuse, moderate alcohol consumption, non-drinker. Survival or death while on CVVHDF was also recorded. For each patient in the study, every drug prescribed during CVVHDF therapy and during the time spent in the ICU prior to starting CVVHDF was recorded. For both groups (prior/during CVVHDF), drugs prescribed were classified into fifteen subcategories according to British National Formulary drug classification.

Indicators of drug use pattern included:

- Mean number of drugs prescribed per patient during and prior to CVVHDF.
- Mean number of anti-infective drugs prescribed per patient during CVVHDF and prior to CVVHDF.
- Percentage of patients prescribed anti-infective drugs/antimicrobial drugs.
- Comparison of numbers of drugs prescribed prior to and during CVVHDF.
- Comparison of drug classes prescribed during versus after CVVHDF therapy.

An overview of the methodologies employed, emanating from this initial audit, is presented as a flow diagram below.

Flow Diagram representing an overview of the general methodologies employed in this pharmacokinetic and clinical study.



2.2 Retrospective Pharmacokinetic Evaluation of Antimicrobial Drugs during CVVHDF

2.2.1 Introduction

The prerequisites for the usefulness of drug concentrations in routine patient care include significant consequences associated with therapeutic failure or toxicity, wide interpatient pharmacokinetic variability, narrow therapeutic range, and the demonstrated utility of drug concentration monitoring as an intermediate end point to guide therapeutic decisions. Aminoglycoside and vancomycin therapy in critically ill patients meet these criteria and so serum concentrations of these antibiotics are routinely monitored for patients in this ICU. 'Peak' and trough concentrations are measured for these drugs throughout CVVHDF therapy and critical illness. These serum drug concentrations are recorded on the patient's drug kardex, in their microbiological reports and on the Hospital Information System (HIS).

2.2.2 Objectives

A retrospective analysis of routine 'peak' and trough concentrations of the study drugs, generated for critically ill patients treated with CVVHDF over a 12 month period, was undertaken. The antibiotics analysed were vancomycin, amikacin and gentamicin.

Therapeutic Drug Monitoring is undertaken with the aim of promoting targeted antimicrobial chemotherapy to improve outcomes and reduce potential toxicity. The aim of this retrospective analysis was to investigate whether routinely collected serum drug concentration data could be used to estimate pharmacokinetic parameters for these drugs during CVVHDF therapy, for the purpose of appropriate dosage adjustment for individual patients.

2.2.3 Ethical Considerations

Ethics Board Approval was obtained from the Joint Hospitals (AMNCH/SJH) Ethics Board Committee, prior to the commencement of this study.

2.2.4 Sample selection

Patients treated with CVVDHF over the time period January to December 2003 were identified from an ICU database. A review of medical, pharmacy and microbiological records for all patients was used to identify patients treated with vancomycin, amikacin or gentamcin during CVVHDF. All critically ill patients treated with vancomycin, amikacin or gentamicin who exhibited haemodynamic instability and ARF requiring CVVHDF therapy over a 12 month period (January-December 2003) were considered for inclusion in this retrospective pharmacokinetic analysis. The criteria for inclusion in the study were (a) availability of demographic, clinical, drug dosage, infusion and blood sampling times to permit calculations of pharmacokinetic values (b) a minimum of two timed drug concentrations (peak and trough) in the same dosage interval (c) critical illness and treatment with CVVHDF.

The patient population was described by recording age, sex, serum creatinine, Acute Physiology and Chronic Health Evaluation (APACHE) II score, maximum Sequential Organ Failure Assessment (SOFA) score, admitting diagnosis and microbiological infection.

2.2.5 Data Analysis

A retrospective audit of drug kardexes, medical charts and computerised reports of microbiologic studies for the selected patients was carried out. Records of CVVHDF conditions were assessed. Details of blood flow rates, dialysis fluid rates and ultafiltration rates were recorded. Data relating to anticoagulation (or coagulopathy), duration of filter use and interruptions to ultrafiltrate flow were also

recorded. A detailed analysis of TDM Data was undertaken, including details of drug administration, sampling times and reported levels, together with microbiological reports. Details of antibiotic administration were analysed; doses, infusion rates, infusion start and stop times for each patient were recorded. When ICU patients are treated with a glycopeptide or an aminoglycoside, the dose and duration of infusion (start and stop times) are recorded in a designated space on the drug kardex. Serum concentration data were only included in the analysis where this critical dosing data had been clearly documented. 'Peak' and trough serum concentrations and sampling times are recorded on the drug kardex and on the Hospital Information System, where drug levels are reported. These records were cross-checked and only when these records were in agreement was the data included.

The concentration of amikacin, gentamicin and vancomycin in serum had been determined by fluorescence polarization immunoassay (TDx; Abbot Diagnostics). An amikacin standard concentration curve was calibrated using calibrators (0, 5.0, 10, 20, 30 and 50 mg/l). Within-run coefficients of variation were less than 4% and between-run coefficients of variation were less than 8%. A vancomycin standard concentration curve was calibrated using calibrators (0, 5.0, 10, 20, 30 and 50 mg/L)

2.2.6 Pharmacokinetic Analysis

Serum concentration-time data were analysed using non-compartmental and single compartment analysis. All C_{pmax} (peak) concentrations included in our analysis were sampled at least one hour after a 2-hour infusion was complete. Half-lives were calculated from the slope of the serum concentration-time semi-log plot. Elimination rate constants were obtained using the equation 1.2.2.7. The volume of distribution was calculated from equation 1.2.6.3. Total Body Clearance (TBC) was calculated from equation 1.2.5.6 (Introduction).

2.3. Prospective Clinical and Pharmacokinetic study of Vancomycin during CVVHDF.

2.3.1. Materials

Trade Name: Vancocin for injection

Qualitative and Quantitative Composition:

Vancomycin hydrochloride, not less than 525,000IU, equivalent to 500mg vancomycin, as an off-white lyophilised plug. Eli Lilly and Company Limited, Basingstoke, Hampshire.

2.3.2 Methods

2.3.2.1 Protocol Design

The study design was a prospective observational open-label pharmacokinetic and clinical evaluation of vancomycin in patients on CVVHDF, set in a medical–surgical intensive care unit.

2.3.2.2 Patient Selection

The patients were recruited from the patient population admitted to the Intensive Care Unit of the Hospital, having obtained fully informed consent from the patient or assent from a relative. The Patient Information Leaflet is included in Appendix 1.

The inclusion criteria were as follows:

- Over 18 years of age
- Patients requiring CVVHDF
- Patients treated with vancomcyin

And the exclusion criteria was

- Patient/ relatives' refusal

2.3.2.3 Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki (1964), amended Hong Kong (1989). The approval of the Joint Hospitals Ethics Committees (St. James Hospital/Adelaide and Meath Hospital Dublin, Incorporating the National Children's Hospital) was obtained. The committees were satisfied as to the objectives of the studies and their design, the investigators qualifications, inclusion/exclusion criteria, receipt of informed consent and the confidentiality of the participants. A clinician obtained consent or assent from the patient or a relative, after informing the patient or relative of all relevant information and providing them with a Patient Information Leaflet describing the study. Both the Consent/Assent forms and the Patient Information Leaflets were approved by the Ethics Board Committee. Consent was given in writing and signed by the participant if deemed capable of comprehending the nature, significance and scope of the consent or by a relative where this was not the case. The consent forms were also signed by or on behalf of the investigator. The confidentiality of patients taking part in the study was preserved. All data was recorded on Patient Record Forms, designed for the study. When a separate file was required for data storage, patient confidentiality was protected by use of patient numbers rather than names.

2.3.2.4 Drug Administration

Vancomycin was administered to the patients in Sodium Chloride Intravenous Infusion B.P. and other drugs were not mixed in the same line. Each dose of Vancomycin was infused intravenously via a central line over a period of at least 60 minutes, depending on the magnitude of the dose. Infusion-related adverse events are related to both concentration and rate of administration of

vancomycin. Concentrations of no more than 5mg/ml were used in this study, as per the SPC recommendations. Infusions were given over at least 60 minutes but if doses exceeding 500mg were used, a rate of infusion of no more than 10mg/min was used. The exact duration of the infusion (infusion start and finish times) was recorded on the Data Collection Form.

2.3.2.5 CVVHDF conditions

Continuous veno-venous haemodiafiltration was generally performed with 1 L/hr dialysate and 2 L/hr predilution filtration solution, producing 3 L/hr dialysis effluent. Where there was deviation from these dialysate fluid and ultrafiltration rates, or where other conditions were prescribed, based on patient requirements, these changes in dialysate and/or ultrafiltration rates were recorded accurately. The blood was pumped at 200ml/min using a Gambro BMM-10 blood pump (Gambro) using an extra-corporeal circuit containing a Hospal AN69HF haemofilter (Hospal). Unless anticoagulation was contraindicated, anticoagulation of the circuit was titrated to patient requirement.

2.3.2.6 Clinical Parameters

The Acute Physiology and Chronic Health Evaluation II Score (APACHE II), (SOFA) and several other clinical parameters were recorded on a daily basis.

2.3.2.7 Specimen collection

A. Blood Samples

Blood samples (7ml) were collected in centrifuge tubes from an indwelling arterial cannula. The first sample (C_{pmin}) was taken immediately prior to the intravenous administration of vancomycin and further samples were taken at intervals of 1 hour, 2 hours, 4 hours, 6 hours, 9 hours, 12 hours and 18 hours after the infusion was complete. In some cases, there was slight deviation from

the designated sampling times for clinical reasons and where this occurred the exact sampling time was recorded and used in all calculations. All blood samples were stored at 4 degrees Celsius prior to prompt centrifugation. Serum samples were stored at -80 degrees Celsius until analysed.

B. Effluent Fluid Collection

Dialysis effluent (ultafiltrate/dialysate) was collected for a complete dosage interval for each patient recruited. The volume of each hourly batch of effluent was recorded and a 40ml sample was taken for analysis. Aliquots from each sample were analysed for vancomycin concentration and creatinine determination. In addition, each time the ultrafiltration collection unit was emptied, the volume was recorded and an aliquot was taken for vancomycin analysis. All effluent samples were stored at +4 degrees celcius pending assay.

2.3.2.8 Analytical Procedures

The concentration of vancomycin in serum and dialysis effluent (dialysate/ultrafiltrate) was determined by Fluorescence Polarisation Immunoassay (TDx; Abbot Diagnostics) in the routine Microbiology Laboratory using in the Hospital. A vancomycin standard concentration curve was calibrated using calibrators (0, 5.0, 10, 20, 30, 50mg/L).

2.3.2.9 Pharmacokinetic Analysis

Vancomycin serum concentration data was fitted first to a two-compartment model (sum of two exponential functions) and then to a one-compartment model (single exponential function) according to equations 1.2.4.1 and 1.2.7.1 respectively, using Micromath Software, Scientist Version 3.0. Goodness of fit was assessed by comparison of the Model Selection Criterion (MSC), the coefficient of determination (r^2) and correlation coefficient. Best-fit parameters and estimates of vancomycin pharmacokinetic parameters were compared for both models. Model-

independent methods (non-compartmental methods) were also used to obtain estimates of the volume of distribution. Estimates of pharmacokinetic parameters obtained using multiple serum concentrations in a dosage interval were compared with those calculated from two serum concentrations in a dosage interval. Vancomycin clearance by CVVHDF was investigated for a single dosage interval for each patient. The amount of vancomycin in each effluent (ultrafiltrate/dialysate) collection was calculated by multiplying the ultrafiltrate vancomycin concentration by the volume of the collection. The amount of vancomycin removed by the filter during the CVVHDF period (A_{CVVHDF}) was calculated as the sum of the products of concentration and volume for each collection period. The clearance of vancomycin by CVVHDF was determined as $Cl_{CVVHDF} = A_{CVVHDF} / AUC_{CVVHDF}$. The percentage of vancomycin eliminated by CVVHDF was calculated as $F_{CVVHDF} = 100\% \times Cl_{CVVHDF}/Cl$. The total amount of creatinine removed by the filter was calculated in an analogous method to that used for estimating vancomycin removal, from the sum of the products of the effluent volumes and creatinine concentrations in each collection period. The clearance of creatinine by CVVHDF (Cl_{Creat}) was calculated as $Creat_{effluent}.Volume_{effluent}$ / SerCr .1440, where the dosage interval was 24 hours. A sieving coefficient for creatinine was also calculated from matched hourly serum and effluent creatinine concentrations. Similarly, a sieving coefficient (S_{vanc}) was calculated from time-matched vancomycin serum and effluent concentrations, according to the equation $S_{vanc} = C_{effleunt}/C_{serum}$.

2. 4. Prospective Clinical and Pharmacokinetic study of Aminoglycosides during CVVHDF.

2.4.1. Materials

Amikacin

(1) Amikin injection 100mg/2ml (2) Amikin injection 500mg/2ml

Qualitative and Quantitative composition:

(1) Each vial contains amikacin sulphate equivalent to amikacin activity 100mg (100,000 international units) in 2ml (50mg/ml).

(2) Each vial contains amikacin sulphate equivalent to amikacin activity 500mg (500,000 international units) in 2ml. Excipients: Each vial contains 14.74mg (0.64mmol) sodium.

Bristol-Myers Squibb Holdings Ltd, trading as Bristol-Myers Pharmaceutical, Swords, Co. Dublin

Excipients: Sodium citrate, Sodium bisulphite (E222), Sulphuric acid, WFI

Gentamicin

Trade Name: Gentamicin Injectable

Qualitative and Quantitative Compositon:

Gentamicin sulphate Ph. Eur. Equivalent to 4.0% w/v (80mg) gentamicin base.

Pharmaceutical Form: Solution for injection: Each ampoule contains a sterile, clear, colourless to pale yellow liquid. The solution is preservative free.

Marketing Authorisation Holder: Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, UK

Excipients: Water for Injection, Sulphuric acid.

2.4.2 Methods

2.4.2.1 Protocol Design

The study design was a prospective observational open-label pharmacokinetic and clinical evaluation of the aminoglycoside antibiotics; amikacin and gentamicin, in patients treated with CVVHDF, set in a medical–surgical intensive care unit.

2.4.2.2 Patient Selection

The patients were recruited from the patient population admitted to the Intensive Care Unit of the Hospital, having obtained fully informed consent from the patient or assent from a relative. The Patient Information Leaflet is included in Appendix 1.

The same inclusion and exclusion criteria were applied to this study as had previously been used for patient selection in the Vancomycin Prospective Study.

2.4.2.3 Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki (1964), amended Hong Kong (1989), as described for the Vancomycin Prospective Study (2.3.2.3).

2.4.2.4 Drug Administration

Amikacin /Gentamicin were administered via a central line and other drugs were not mixed in the same line. Each dose was infused intravenously over a period of 30 minutes. The exact infusion rate and duration of the infusion (infusion start and finish times) were recorded on the Data Collection Form.

2.4.2.5 CVVHDF conditions

Continuous veno-venous haemodiafiltration was generally performed with 1 L/hr dialysate and 2 L/hr predilution filtration solution, producing 3 L/hr dialysis effluent. Where there was deviation from these dialysate fluid and ultrafiltration rates, or where other conditions were prescribed, based on patient requirement, these changes in

dialysate and/or ultrafiltration rates were recorded accurately. The blood was pumped at 200ml/min using a Gambro BMM-10 blood pump (Gambro) using an extra-corporeal circuit containing a Hospal AN69HF haemofilter (Hospal). Unless anticoagulation was contraindicated, anticoagulation of the circuit was titrated to patient requirement.

2.4.2.6 Clinical Parameters

APACHE II, SOFA scores and several other clinical parameters were recorded on a daily basis.

2.4.2.7 Specimen Collection

A. Blood Sampling

Blood samples (7ml) were collected in centrifuge tubes from an indwelling arterial cannula. 'Peak' concentrations (30 minutes after the infusion was complete) and C_{pmin} (trough) concentrations were recorded for each dosage interval. Additionally, multiple serum concentrations (minimum of seven) in a dosage interval were obtained for at least one dosage interval for each patient. The first sample (C_{pmin}) was taken immediately prior to the intravenous administration of amikacin/gentamicin and a minimum of six further samples were taken; the first immediately after infusion completion (C_{pmax}), then at 1 hour, 2 hours, 5 hours, 8 hours, 12 hours and 18 hours. At certain time points for some patients, it was not feasible to take a serum sample at the designated time. This possibility had been pre-empted during the study design and during induction all individuals involved in sampling had been advised to take a serum sample as close to the designated time as practical but to record accurately (to the nearest minute) the actual sampling time. This policy was adhered to throughout the study and although there was some deviation from the prescribed sampling strategy, a minimum of seven accurately timed serum samples were obtained for all patients. All blood samples were stored at 4 degrees Celsius prior to prompt centrifugation.

B. Effluent fluid collection

Effluent fluid (ultrafiltrate/dialysate) was collected for a complete dosage interval. The volume of each hourly batch was recorded and a 40ml sample was taken for analysis. Aliquots from each sample were analysed for aminoglycoside (amikacin/gentamicin) concentration and for creatinine determination. Each time the ultrafiltration collection unit was emptied, the volume was recorded and an aliquot was taken for analysis. Additionally, for the dosage interval in which the multiple serum aminoglycoside concentrations were obtained, effluent samples were collected for aminoglycoside determination at the same time points to allow calculation of sieving coefficients. All effluent samples were stored at +4 degrees celcius pending assay.

2.4.2.8 Analytical Procedures

The concentrations of amikacin/gentamcin in serum and effluent fluid (dialysate/ultrafiltrate) were determined by Fluorescence Polarisation Immunoassay (TDx; Abbot Diagnostics) in the main Microbiology Laboratory in the Hospital. An amikacin standard concentration curve was calibrated using calibrators (0, 5.0, 10, 20, 30, 50mg/L).

2.4.2.9 Pharmacokinetic Analysis

Amikacin serum concentration data was fitted to a one-compartment model (single exponential function) and two-compartment model (sum of two exponential functions), using Micromath Software, Scientist Version 3.0. Best fit parameters and estimates of pharmacokinetic parameters were compared for each model. Estimates of pharmacokinetic parameters derived from multiple serum concentrations in a dosage interval were compared with those calculated using peak and trough serum concentrations only.

Aminoglycoside (amikacin/gentamicin) clearance by CVVHDF was investigated for a single dosage interval for each patient. The amount of amikacin/gentamicin in each

effluent (ultrafiltrate/dialysate) collection was calculated by multiplying the ultrafiltrate amikacin/gentamicin concentrations by the volume of the collection. CVVHDF clearance was calculated as $Cl_{CVVHDF} = A_{CVVHDF} / AUC_{CVVHDF}$. The percentage of drug eliminated by CVVHDF was calculated as $F_{CVVHDF} = 100\% \times Cl_{CVVHDF}/Cl$. The creatinine concentration in effluent for each hour of a specified dosage interval was also directly measured. The volume of effluent collected was used to calculate the total amount of creatinine removed by the filter during a dosage interval. The clearance of creatinine by CVVHDF (Cl_{Creat}) was calculated as $Creat_{effluent.}Volume_{effluent}$ / SerCr .1440, where the dosage interval was 24 hours. A sieving coefficient (S_{amik}) was calculated from the mean amikacin concentration in effluent and mean amikacin/gentamicin concentration in serum for each 2-hour interval: $S_{amik} = C_{effleunt}/C_{serum.}$

2.5. Prospective Pharmacokinetic and Clinical Study of Ciprofloxacin during CVVHDF.

2.5.1. Materials

Ciprofloxacin Trade Name: (1) Ciproxin Solution for Infusion 50ml (2) Ciproxin Solution for Infusion100ml (3) Ciproxin Solution for Infusion 200ml
Qualitative and Quantitative Composition:

(1) 100mg Ciprofloxacin (as lactate) in a 50ml solution (2mg/ml)

(2) 200mg Ciprofloxacin (as lactate) in a 100ml solution (2mg/ml)

(3) 400mg Ciprofloxacin (as lactate) in a 200ml solution (2mg/ml)

Pharmaceutical Form: (1) Solution for Infusion, Type 2 (Ph. Eur.) infusion bottle containing 50ml of a clear, yellowish, solution for infusion. (2) Solution for Infusion, Type 2 (Ph. Eur.) infusion bottle containing 100ml of a clear, yellowish, solution for infusion. (3) Solution for Infusion, Type 2 (Ph. Eur.) infusion bottle containing 200ml of a clear, yellowish solution for infusion.
Marketing Authorisation Holder: Bayer plc., Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, United Kingdom.
Marketing Authorisation Number: PA 21/36/2
Excipients: Lactic acid (0.01%), Sodium Chloride, Concentrated HCL, WFI.

2.5.2 Methods

2.5.2.1 Protocol Design

The study design was a prospective observational open-label pharmacokinetic and clinical evaluation of ciprofloxacin in patients on CVVHDF, set in a medical–surgical intensive care unit.

2.5.2.2 Patient Selection

The patients were recruited from the patient population admitted to the Intensive Care Unit of the Hospital, having obtained fully informed consent from the patient or assent from a relative. Patient Information Leaflets and Consent Forms are included in Appendix 1. The inclusion criteria were those applied in the previous prospective studies of vancomycin and the aminoglycosides.

2.5.2.3 Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki (1964), amended Hong Kong (1989). The approval of the Joint Hospitals Ethics Committee (St. James Hospital/Adelaide and Meath Hospital Dublin, Incorporating the National Children's Hospital) was obtained. Serum concentrations of ciprofloxacin are not routinely monitored in this Hospital. Patients or a relative, where the patient was unable to give consent, were informed of this fact. A Clinician obtained consent or assent from the patient or a relative, after informing the patient or relative of all relevant information and providing them with a Patient Information Leaflet describing the study. Both the Consent/Assent forms and the Patient Information Leaflets were approved by the Ethics Board Committee. The confidentiality of patients taking part in the study was preserved. All data was recorded on Patient Record Forms, designed for the study. When a separate file was required for data storage, patient confidentiality was protected by use of patient numbers rather than names.

2.5.2.4 Drug Administration

Ciprofloxacin was obtained as Ciprofloxacin hydrochloride monohydrate from Bayer UK.

2.5.2.5 CVVHDF conditions

Continuous veno-venous haemodiafiltration was performed with 1 L/hr dialysate and 2 L/hr predilution filtration solution, producing 3 L/hr dialysis effluent. Where there was deviation from these dialysate fluid and ultrafiltration rates, or where other conditions were prescribed, based on patient requirement, these changes in dialysate and/or ultrafiltration rates were recorded accurately. The blood was pumped at 200ml/min using a Gambro BMM-10 blood pump (Gambro) using an extra-corporeal circuit containing a Hospal AN69HF haemofilter (Hospal). Unless anticoagulation was contraindicated, anticoagulation of the circuit was titrated to patient requirement.

2.5.2.6 Clinical Parameters

APACHE, SOFA scores and several other clinical parameters were recorded on a daily basis.

2.5.2.7 Specimen Collection

A. Blood Sampling

Blood samples (7ml) were collected in centrifuge tubes from an indwelling arterial cannula. The first sample (C_{pmin}) was taken immediately prior to the intravenous administration of ciprofloxacin and further samples were taken at the time point when the infusion was complete (t = 1 hour) and at intervals of one hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours and 12 hours after the infusion was complete, where the dosage interval was 12 hours. For patients, where the prescribed dosage interval was 24 hours, serum samples were also taken at 15, 18 and 24 hours. For all samples, the exact sampling time was recorded on the (Data Collection Form) DCF. All blood samples were stored at

4 degrees Celsius prior to prompt centrifugation. Serum samples were stored at -80 degrees Celsius until analysed.

B. Effluent Fluid Collection

Dialysis effluent (ultafiltrate/dialysate) was collected for a complete dosage interval. The volume of each hourly batch was recorded and a 40ml sample was taken for analysis. Aliquots from each sample were analysed for ciprofloxacin concentration and for creatinine determination. As a control measure, each time the effluent fluid collection bag was emptied, the volume collected was recorded and a sample was taken for an analysis. Timed effluent fluid samples were also taken to coincide with the timed multiple serum samples in a dosage interval.

2.5.3 Determination of Ciprofloxacin Concentrations

Ciprofloxacin concentration in serum and ultafiltrate/dialysate fluid was determined by High Performance Liquid Chromatography (HPLC). The assay method was an adaptation of a method by Davis et al (74),

2.5.3.1 Ciprofloxacin Serum and Effluent Fluid Assay

Reagents and Solutions:

Ciprofloxacin hydrochloride monohydrate, Ciproxin IV formulation (Bayer UK),

Tetrabutylammonium hydrogen sulphate,

Orthophosphoric acid (85%),

Acetonitrile (HPLC-grade),

HPLC-grade water was used throughout the procedure.

All other solvents were analytical grade.

The internal standard solution was prepared as a 20μg/ml solution of β-hydroxypropyl theophylline in phosphate buffer pH 7.4. Further dilution was

carried out with phosphate buffer (pH 7.4) to an appropriate working concentration.

The mobile phase was acetonitrile-salt solution (15:85, v/v). 1L of mobile phase was prepared as follows: Initially 1L of the salt solution was made up using the following quantities of each salt: 4.54g KH_2PO_4 , 5.94g $Na_2HPO_4.2H_2O$ and 1.49g $(n\text{-}C_4H_9)_4N^+HSO_4^-$.

150 mls of acetonitrile was added to 850 mls of the salt solution. Orthophosphoric acid was added dropwise until the pH was adjusted to 3. The stationary phase was a Spherisorb S5 ODS2 column (Hicron, 25cm x 4.9 mm I.D.) fitted with a Spherisorb ODS 10mm x 4.9mm I.D. guard column. Analysis of the UV spectra range for ciprofloxacin was undertaken. The compound was found to absorb strongly with the peak of maximum absorbance occurring at a wavelength of 276nm. Thus, it was concluded that UV detection carried out at 280nm was appropriate.

2.5.3.2 Assay procedure

Blood samples were collected in 7ml centrifuge tubes. Once samples were taken they were cooled to +4 degrees Celsius and maintained at this temperature until transferred to the laboratory. Blood samples were promptly centrifuged and serum samples were stored at -80 degrees Celsius until analysed.

Fifty µl of the internal standard solution, 100µl of phosphate buffer and 5ml of chloroform-propan-2-ol (95:5%v/v) was added to 100µl of serum. This was subsequently mixed by shaking on a rotary mixer for 15 minutes. The mixture was centrifuged at 800 g for 5 minutes to separate the layers. The aqueous layer was aspirated off and discarded. The organic layer was evaporated under

nitrogen at 45 degrees Celsius. The dry residue was then reconstituted by sonication with 100µl of mobile phase. A 25µl aliquot was analysed by HPLC. Direct injection of the ultrafiltrate samples onto the HPLC column was possible, as these samples are protein free.

A calibration graph using known concentrations of ciprofloxacin in control serum was prepared. Calibration standards for the serum samples were prepared by spiking drug free serum with ciprofloxacin. Analyses were preformed with 100µl of standard solutions, containing Ciprofloxacin in phosphate buffer (pH 7.4), added to 100µl of blank serum and 50µl of internal standard. These mixtures were treated as above. Because of light sensitivity of the fluoroquinolones, all calibration standards were freshly prepared every day. The peak:height ratio of ciprofloxacin to β-hydroxypropyl theophylline was plotted against the known concentration of ciprofloxacin added. The concentration of ciprofloxacin in the study samples was then calculated using the regression parameters obtained from the calibration graph.

Quantitation was based on external standard calibration using the ratio of the peak areas of the analyte and the internal standard. For the quantitation of serum samples, spiked serum with analyte concentrations between 0.1 and 20.0 µg/ml was used for the calibration curve. Calibration curves for ultrafiltrates were generated by measuring ciprofloxacin standards in blank dialysis fluid in a concentration range of 0.1 -20 µg/ml. The within- and between-day accuracy and precision were calculated by measuring spiked serum samples and ciprofloxacin standards in phosphate buffer at three different concentrations in triplicate on three different days. The accuracy was calculated as the percentage of the determined concentration form the nominal ones. The precision was given as the relative standard deviation (R.S.D. %). The limit of

detection was given as determined by a signal-to-noise ratio of 3. Ciprofloxacin recovery from control blood was determined by slope comparison of extracted and non-extracted calibration curves. Replicate analysis was preformed both on control samples and study samples to eliminate batch variations.

Ciprofloxacin hydrochloride monohydrate (1g) was obtained as a gift from Bayer UK. This was used to verify the concentration of the commercial infusion solution Ciproxin.

2.5.3.3 Pharmacokinetic Analysis

Serum concentration-time data for ciprofloxacin were analysed by standard non-compartmental methods. Elimination of drugs was assumed to be first-order. C_{pmax} was directly observed as the maximum measured concentration. The apparent terminal elimination rate constant (k_{el}) was determined by least-squares regression analysis of the terminal portion of the natural log concentration-time curve. Half-life was calculated using equation 1.2.2.7. The maximum drug concentration in serum (C_{pmax}) was directly observed. The area under the concentration-time curve from zero to the end of the dosing interval (AUC_{0-n}) was calculated using the linear trapezoidal summation method. The total 24-hour AUC was calculated by AUC_{0-12} X 2, for patients receiving ciprofloxacin every 12 hours. Total body clearance of ciprofloxacin was calculated using equation 1.2.9.1. The Volume of Distribution at steady-state was calculated according to equation 1.2.9.4.

For each patient, ciprofloxacin concentrations in effluent were determined for a single dosage interval. The ciprofloxacin concentration in effluent for each hour of the study period was determined by measurement of the hourly effluent samples collected. The volume of effluent produced in each hour was

measured. The clearance of creatinine by CVVHDF was also calculated at hourly intervals.

Sieving coefficients for ciprofloxacin and creatinine were calculated from the time-matched concentrations in effluent and in serum for a single dosage interval, whereby $S_{creatinine} = C_{effluent}/C_{serum}$ and $S_{cipro} = C_{effluent}/C_{serum}$. The clearance of creatinine was calculated from $S_{creatinine}$ and the measured flow of effluent where $Cl_{creat} = S_{creat}$ X Q. Ciprofloxacin clearance was calculated in an analogous method. Cl_{cipro} and Cl_{creat} were monitored at 2-hourly intervals over the 12-hour study period in an attempt to detect any change in filter performance over time.

2.6. Infective Pathogens and Antimicrobial Usage in ICU Patients treated with CVVHDF: a preliminary investigation of the impact of antimicrobial prescribing on the incidence of multi-drug resistant strains.

An investigation of the type and prevalence of infective micro-organisms and the incidence of antimicrobial resistance in patients treated with CVVHDF over the 24-month period; January 2004 to December 2005, was undertaken.

2.6.1 Objectives:

(1) To determine the most frequently isolated pathogens among critically ill patients treated with CVVHDF.

(2) To investigate antimicrobial resistance amongst bacterial isolates obtained from patients in Intensive Care Units (ICU) treated with CVVHDF

(3) To examine antibiotic usage in patients where multidrug resistance pathogens were identified

2.6.2 Methodology

This was a retrospective ICU-based surveillance study involving all patients treated with CVVHDF over a 24 month period, from January 2004 to December 2005. All patients treated with CVVHDF for whom antimicrobial consumption data and antimicrobial resistance data were available, were eligible for inclusion in the analysis. Patients treated with CVVHDF were identified from the ICU database designed for this purpose.

(1) Data was collated from the Hospital Infection Surveillance System and Patients' Medical Records, Drug kardexes and Microbiological records.

(2) Nosocomial infections among critically ill patients treated with CVVHDF were analysed by infection site, pathogen distribution and drug therapy.

Data was analysed using SPSS. In-hospital mortality rates among patients with blood stream infections due to multi-drug resistant strains and patients without these infections were analysed using chi-squared tests. For all statistical tests, a significance level of 0.05 was considered significant. Mean values are quoted as mean +/- standard deviation.

2.7. Statistical Analysis

Throughout this thesis, all values are expressed as the mean +/- standard deviation (continuous variables) or as a percentage of the group from which they were derived (categorical variables). All p-values were two-tailed, and p=0.05 was considered to indicate statistical significance. Continuous variables were compared using the Student's t test for normally distributed variables and the Wilcoxon rank-sum test for non-normally distributed variables. The χ^2 test was used to compare categorical variables.

Chapter 3: An Investigation of Drug Use and Prescribing Practice during Continuous Venovenous Haemodiafiltration (CVVHDF)

3.1 Demographic Data and Clinical Characteristics:

During the 12 month period, January – December 2003, forty two patients were treated with CVVHDF. Thirty nine patients were included in the study. The medical notes for the three excluded patients were missing (n=1), incomplete (n=1) or unavailable (n=1). The proportion of female patients (0.58) treated with CVVHDF was higher than male patients. The mean age of patients starting CVVHDF was 60.12 +/- 15.40 years. This high mean age may reflect the increased susceptibility of the elderly to renal failure, due to pre-existing but often undiagnosed renal impairment or pre-existing disease states which contribute to the development of Acute Renal Failure (ARF) and are more common in the elderly. Examples of such disease states encountered in this sample included acute pancreatitis, autoimmune hepatitis and ESRF. More than half the patients were current (42.4%) or ex-smokers (15.2%). This is clinically relevant as the link between smoking and peripheral vascular disease leading to renal ischemia has been well documented and renal ischemia is a major risk factor for the development of ARF (75). 18.2% of patients had a history of alcohol abuse. Excessive alcohol consumption can precipitate disease states such as pancreatitis and cholestatic liver disease, which were the presenting disease states in 11.1% of patients in the sample. The proportion of patients classified as medically obese was 27.8%. Obesity presents problems for designing dosage regimens, in particular for anesthetics and antibiotics where dosing is based on body weight (10). As these patients are immobile and sedated, it is difficult to obtain regular measurements of weight and so dosing

is often based on ideal body weight, which will obviously vary from actual body weight in obese patients. Patients (n=39) presented with a diverse range of disease states (n= 23). The diverse range of admission disease states highlights the variability of clinical presentations culminating in Acute Renal Failure. It also demonstrates the difference in presentation of 'critical illness ARF' to the less common 'medical ARF' occurring on the general ward which presents as specific renal disease. Decompensated alcoholic liver disease was the most frequent presenting disease state (n=5). Abdominal Aortic Aneurysm (AAA), End-stage renal failure (ESRF) and small bowel obstruction were the next most common conditions (n = 3). Lower respiratory tract infection was the reason for admission for two patients.

Table 3.1: Disease State on Admission to ICU for Patients treated with CVVHDF (n=39).

Disease State on Admission	Frequency
Decompensated alcoholic liver disease	5
End Stage Renal Failure (ESRF)	3
AAA rupture	3
Small bowel obstruction	3
Lower respiratory tract infection	3
Acute cholecystitis	2
Acute on chronic renal failure	2
Multiple trauma (post RTA)	2
Acute pancreatitis 2y gallstones	1
Acute renal failure (vasculitis/hypercalcaemia/acute interstitial nephritis)	1
Autoimmune hepatitis	1
Cellulitis (post-op infection)	1
Legionella pneumonia	1
Metastatic colorectal cancer	1
Multiple myeloma	1
Multiple stab wounds	1
Necrotic diverticulitis	1
Osteoporosis	1
Pancreatitis secondary to alcohol abuse	1
Pre-renal azotemia secondary to heart failure	1
Rhabdomyolysis secondary to acute allergic reaction	1
Right lung lesion-investigative admission	1
Total hip replacement	1
Type 1 respiratory failure	1

The mean duration of CVVHDF therapy was 8.3 days (Range = 1- 34 days).

The reasons for starting CVVHDF therapy included ARF, sepsis, fluid

overload, metabolic acidosis and ESRF, where haemodialysis was not tolerated. ARF and sepsis were the major reasons for starting CVVHDF in this patient sample. Sepsis is defined as a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms. Severe sepsis can be associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or an acute alteration in mental status. Sepsis may be caused by Gram-negative and Gram-positive bacteria, fungi, protozoa, Rickettsia, viruses and spirochetes. This audit identified common infective Gram positive organisms as Coagulase negative staphylococci (18%), Staphylococcus aureus (15%), Enterococcus speices (15%) and Clostridium difficile (9%). Gram negative organisms include Escherichia coli (12%), Pseudomonas aeruginosa (12%), and Klebsiella species (15%).

Nosocomial infection rates in ICU patients are 5-10 times higher than among general ward patients (76). Many infections acquired in the ICU are endogenous and follow colonization of the alimentary tract by organisms usually insignificant in healthy individuals. Among the four patients admitted with alcoholic liver disease, sepsis was the cause of decompensation in three patients with chronic liver disease. In two patients, the site of sepsis was known but in the third primary spontaneous bacterial peritonitis was diagnosed, due to signs of sepsis, worsening encephalopathy and unexplained general deterioration. The infecting organism in all cases was a Gram-negative anaerobe, with Escherichia coli cultured for one patient and Pseudomonas aeruginosa isolated for the other two patients.

Drug toxicity contributed to four cases of acute renal failure. In three patients, this involved the administration of nephrotoxic drugs, while in the fourth patient, rhabdomyolysis secondary to an acute allergic reaction (to quinine) culminated in the development of ARF. The nephrotoxic drugs implicated were Non-steroidal Anti-inflammatory Drugs (NSAIDs), cyclophosphamide, ACE inhibitors and diuretics. The administration of NSAIDs was responsible for precipitating ARF in two patients. Diclofenac contributed to ARF in a patient with mild pre-existing renal impairment receiving concurrent frusemide. The co-administration of two nephrotoxic drugs to a patient with pre-existing renal impairment was an unexpected finding. More than one third of patients who develop ARF in ICUs have chronic renal dysfunction due to factors such as age-related changes, long-standing hypertension, diabetes or atheromatous disease of the renal vessels (75). It may manifest as a raised serum creatinine but this is not always the case. In some cases, when patients are receiving vancomycin or aminoglycoside therapy, therapeutic drug monitoring may reveal impaired drug elimination, as an initial sign of renal impairment. Often, what may seem to the clinician to be a relatively trivial insult (e.g. administration of a nephrotoxin), which does not fully explain the the onset of ARF in a normal patient is sufficient to unmask lack of renal function reserve in a patient with chronic renal dysfunction. This was highlighted in the case of this patient and the need for caution in prescribing nephrotoxins, such as diclofenac, was emphasised. A combination of mefenamic acid and diclofenac were responsible for precipitating ARF in the second patient. These drugs had been prescribed in the community prior to hospital admission. Both cases suggest that prescribing guidelines should be continually reviewed, with the intention of cautioning the use of NSAIDs in patients with renal or cardiac

risk factors. An acute allergic reaction to quinine resulted in rhabdomyolysis culminating in acute renal failure in one patient. Cyclophosphamide precipitated ARF in a further patient.

3.2 Analysis of Drug Classes prescribed prior to and during CVVHDF

The mean number of drugs prescribed per patient during CVVHDF was 14.3 drugs, while the mean number prior to starting CVVHDF was 13.6. The increase in drug consumption during CVVHDF reflects an increase in the use of antimicrobials during CVVHDF. Sepsis requiring aggressive antimicrobial therapy was the most common reason for starting CVVHDF (Percentage of patients = 39.4%). Table 3.2 summarises the mean number of drugs, consumed per patient, in each BNF drug class.

Table 3.2: Comparison of BNF Drug Classes prescribed prior to and during CVVHDF therapy.

Drug Class	No. of drugs per patient prior to CVVHDF (mean +/- sd)	No. of drugs per patient during CVVHDF (mean +/- sd)
Anti-infectives	3.39 +/- 3.20	4.70 +/- 2.66
Cardiovascular	2.73 +/- 2.31	2.88 +/- 1.80
CNS	2.42 +/- 1.87	1.00 +/- 1.75
Gastrointestinal	1.64 +/- 0.96	1.36 +/- 0.93
Nutrition/Blood	0.94 +/- 1.35	1.55 +/- 1.12
Endocrinology	0.69 +/- 0.90	0.56 +/- 0.67
Anaesthesia	0.48 +/- 1.09	1.61 +/- 0.76
Respiratory	0.82 +/- 1.19	0.73 +/- 0.57
Musculoskeletal	0.31 +/- 0.59	0.03 +/- 0.17
Drugs per patient	13.61 +/- 6.19	14.28 +/- 6.77

3.2.1 Anti-infectives

The most commonly prescribed drug class was anti-infectives. Patients requiring intensive therapy are very susceptible to infection due to acquired defects in host defence mechanisms from the immunosuppressive effects of anaesthesia, surgery and drug therapy, the use of invasive monitoring techniques and the severity of the underlying illness requiring admission. The use of broad-spectrum antibiotics, which alter normal bacterial flora, may predispose to infection with resistant organisms. Pneumonia, lower respiratory tract infection, urinary tract infection and blood stream infection were the most frequent types of infection reported. The most frequently reported organisms were Coagulase negative staphylococci (18%), Staphylococcus aureus (15%), Enterococcus species (15%), Klebsiella species (15%), Escherichia coli (12%) and Pseudomonas aeruginosa (12%). A comparison of data collated in this study, with data collected in 2000, revealed an increase in antimicrobial consumption during CVVHDF in 2003. Table 3.3 compares the frequency of prescribing of the most commonly used antimicrobials in both years. The overall usage of antimicrobials, among this patient group treated with CVVHDF, increased by 39% in the three year time period.

Table 3.3: Comparison of antimicrobials prescribed during CVVHDF in 2000 and 2003

Anti-infective drug	% Frequency Patients in 2003 (n = 39)	% Frequency Patients in 2000 (n =14)
Vancomycin	65.6	21.7
Ciprofloxacin	56.3	34.8
Metronidazole	49.0	47.8
Piperacillin/Tazobactam	47.1	34.8
Meropenem	31.3	8.7
Amikacin	24.2	0
Gentamicin	15.2	34.8
Fluconazole	15.6	0
Linezolid	12.2	0
Ceftazidime	9.0	28.6
Co-amoxiclav	9.0	28.6
Erythromycin	6.0	13.0
Teicoplanin	6.0	0.0

The most commonly prescribed antimicrobial was Vancomycin. Vancomcyin is renally eliminated and its half-life is dramatically increased in renal impairment (77). As its molecular weight, plasma protein binding and apparent volume of distribution are low, it is a likely candidate for clearance by CVVHDF. Drug clearance by CVVHDF will result in a potential risk of underdosing patients during CVVHDF therapy, if guidelines for dosage reduction in renal impairment are applied. Linezolid is a reserve antibiotic which was unlicensed in the Republic of Ireland in 2000 but was issued a Product Authorisation in 2003 and so became available for clinical use. Increased usage of Vancomycin, Linezolid and Teicoplanin, which are all commonly used to treat MRSA, may be indicative of MRSA prevalence,

among this patient sample. Vancomycin dosing varied considerably among patients treated with CVVHDF, doses varied from 0.75mg to 1.5g and dosage intervals ranged from 12 hours to 52 hours. The most commonly prescribed regimen was 1g every 24 hours. There is limited published data on Vancomycin dosing during CVVHDF and considerable variability in the range of recommended doses. Given the increased incidence of MRSA in the Hospital and the associated increase in Vancomycin use, optimisation of its dosing in this vulnerable patient group is essential.

Ciprofloxacin, a fluoroquinolone, was widely used as empirical or directed therapy for a variety of infections in these patients due to its excellent activity against common gram-negative pathogens as well as moderate activity against gram-positive organisms. However, the pharmacokinetics of ciprofloxacin in critically ill patients on CVVHDF has not been adequately characterised, despite the prevalence of its use in these patients. An increase in usage of Ciprofloxacin was observed, reflecting its activity against common nosocomial gram-negative pathogens such as Pseudomonas aeruginosa or E.coli, its good oral bioavailability allowing oral dosing and good penetration to peripheral infection sites such as bones or soft tissue infections (78, 79). A wide range of dosing schedules has been suggested for ciprofloxacin during critical illness and this was reflected in the doses recorded in this audit. Dosing schedules included 400mg o.d, 200mg o.d, 400mg b.d, 200mg b.d and 200mg t.d.s. The most common regimen was 400mg administered twice daily, which was prescribed for 64% of patients receiving ciprofloxacin during CVVDHF. This level of variation in the prescribing of a drug, whose levels are not routinely monitored, suggests that further pharmacokinetic studies are indicated. Additionally, there are no existing pharmacokinetic studies investigating this

dosing schedule during CVVHDF and so the evidence-base for using such a regimen requires further analysis.

Overall usage of aminoglycosides increased slightly, but there was a major increase in amikacin usage, while gentamicin use declined. Elimination of aminoglycosides, which have a low level of protein binding and low molecular weight, is mainly via the renal route. Dosage regimens most therefore be adjusted in severe renal insufficiency to prevent accumulation of the drug to toxic levels and the associated risk of oto- and nephrotoxiciy. However, these drug characteristics also make them likely to be cleared by CVVHDF and so kinetic studies during the period of CVVHDF are required to optimize dosing regimens to produce therapeutic concentrations.

The use of chart review to obtain data on aminoglycoside usage overcomes errors associated with the use of Daily Defined Doses, which underestimate the use of aminoglycosides in renal patients, where smaller doses are administered. At the time of this audit, there was no published data on aminoglycoside pharmacokinetics during CVVHDF and as a result patients were dosed on the basis of their renal impairment, despite the potential for drug clearance by CVVHDF.

Critically ill patients are at risk of developing generalised yeast infections and fluconazole is increasing in use in the ICU for this purpose. The primary route of elimination of fluconazole is renal with recovery of 80% of the unchanged drug and a further 11% of the drug being recovered as metabolites. In addition, its low protein binding and low molecular weight suggests that fluconazole could be eliminated by CVVHDF. Valtonen et al (80) examined the elimination of fluconazole in six patients with ARF treated with CVVH for 24 hours then with CVVHDF for 24 hours, using an ultrafiltration rate of 1L/hr

and then with CVVHDF using a higher ultrafiltration rate of 2L/hr for a further 24 hours. They found that the half-life of fluconazole was significantly longer in patients during CVVH than during CVVHDF at either ultrafiltration rate. They recommended a single daily dose of at least 200mg fluconazole to maintain therapeutic concentrations during CVVHDF. Among the patients analysed in this audit, six patients were treated concurrently with CVVHDF and fluconzole. All six patients were prescribed 200mg fluconazole once daily. Although the proportion of use of metronidazole was high, its clearance by CVVHF tends not to be clinically significant, as it is primarily hepatically eliminated. The use of cephaolosporins has reduced, whereas the use of piperacillin-tazobactam and meropenem has increased. In-vitro models of haemofiltration and haemodiafiltration have been used to estimate dosage regimens for critically ill patients prescribed cefpirome (61). The sieving coefficients reported for cefpriome, ranging from 0.74 – 0.9, were similar to those reported by Vincent et al (81) in earlier in-vivo studies of cefotaxime, cefuroxime and ceftazidime (0.76, 0.81, 0.95).

Piperacillin was used quite extensively both prior to and during CVVHDF. It was always used in combination with the beta-lactamase inhibitor, tazobactam. Piperacillin is a ureidopenicillin with activity against klebsiella and pneumonia. It is used to treat serious gram-negative infection and is most commonly used to treat bacteraemias, pneumonias, and infections following burns. Its gram-negative activity makes it a useful antimicrobial in the treatment of sepsis and its high level of usage was expected. According to hospital guidelines in AMNCH, a 4.5g dose was given every 12 hours to patients during CVVHDF. This guideline assumes negligible CVVHDF drug clearance as this is the dose recommended for renal impairment. In patients with normal kidney function,

the dosage interval is 6 hours. There appears to be some consensus regarding the use of 12-hourly doses of 4.5g piperacillin/tazobactam during CVVHDF within the Hospital and among the patient sample examined, all patients treated with CVVHDF and piperacillin/tazobactam received a twice daily 4.5g dose. Lignian et al (82) studied the behaviour of piperacillin/tazobactam in six critically ill patients with ARF being treated for serious infections. They concluded that the elimination of piperacillin/tazobactam will become significant if the ultrafiltration rate is greater than 25ml/min or if the ultradifiltration rate is greater than 50ml/min. In this case, total clearance will be in the range observed in patients with a creatinine clearance of 20-40ml/min. Thus, the dosage interval for moderate renal impairment i.e. 8 hours should be used rather than 12 hours. This dosing regimen was not used in AMNCH despite the use of high ultrafiltration rates; patients were given 12 hourly doses.

The high usage of meropenem was unexpected due to its 'reserve antibiotic' status within the hospital. Meropenem is a dimethylcarbamoyl pyrolidinyl derivative of thienamycin with broad spectrum activity. Two studies have demonstrated that haemofiltration contributes to meropemem clearance and dosage adjustment may be required to avoid under dosing. Tegeder et al (83) investigated meropenem pharmacokinetics in nine patients with ARF undergoing CVVH, treated with 500mg meropenem twice to three times daily. They reported that 47.2 +/- 17.2% of the dose was removed by CVVH. Thalhammer et al (84) investigated meropenem pharmacokinetics in nine patients with anuric acute renal failure treated with CVVH using high flux polysulfone membranes (Diafilter-30, Amicon). The investigators recommended a dose of 500mg-1g every 8 hours in patients receiving CVVH.

Giles et al (85) investigated 10 critically ill patients treated with CVVHDF and meropenem. They concluded that a meropenem dose of 1g 12 hourly is adequate in patients treated with CVVH or CVVHDF using an AN69 HF filter. As this is the membrane used in AMNCH, it was surprising that no patient treated with meropenem during CVVHDF was prescribed this dose. Instead, nine patients were treated with 500mg meropenem three times daily, while a further three patients received 1g meropenem three times daily.

In addition to its antimicrobial use, erythromycin was also used as a prokinetic agent in 2000. This practice has been discontinued.

3.2.2 Antimicrobial Prescribing and Therapeutic Drug Monitoring

Generally, it was found that reasons for selecting a particular antimicrobial agent or combination of agents were not documented in the medical notes. In particular, reasons for dosage adjustment were not given or comments on the duration of use of a particular agent were not recorded. A major finding was the failure to exploit data obtained through Therapeutic Drug Monitoring. Although, serum drug levels are routinely measured for antimicrobials with a narrow therapeutic index (i.e. vanocmycin, amikacin, gentamicin and teicoplanin), this data is not subsequently subjected to pharmacokinetic analysis which would allow dosage regimens to be optimised and ensure evidence-based prescribing. In addition, a significant proportion of levels (50%) are 'random' levels taken without accurate records of sampling times, which are difficult to interpret pharmacokinetically and have no real use in guiding patient care. A recommendation of this study is that any levels taken should be assessed initially for appropriateness in terms of timing and the levels measured should then be analysed and used to ensure that doses prescribed will result in therapeutic drug levels. This will require education of

both clinicians and nursing staff and the development of protocols, which emphasise the importance of avoiding therapy failure through subtherapeutic dosing and drug toxicity which can impact further on organ function in these critically ill patients. In addition, the need for careful interpretation of measured serum concentrations with particular emphasis on their application to guiding drug therapy must be addressed.

3.2.3 Cardiovascular drugs and DVT prophylaxis during CVVHDF

The most commonly prescribed cardiovascular drugs were cardiac stimulants (adrenaline, noradrenaline and dobutamine) and anticoagulants (heparin, enoxaparin and danaparoid). Anticoagulants are used to prevent clotting of the extracorporeal circuit unless contraindicated for a particular patient. However, in 48% of patients, CVVHDF was run 'heparin-free', without an anticoagulant, as the patients' INRs and aPTTRs were such that an anticoagulant was not necessary. There was a 50% increase in the number of patients receiving conventional unfractionated heparin during CVVHDF (to 35%) compared to prior to starting CVVHDF. This is because heparin is the preferred anticoagulant for the prevention of clots in the extracorporeal circuit of CRRT apparatus. 9% of patients were prescribed enoxaparin, a low molecular weight heparin with a longer duration of action than heparin. There was one case of heparin-induced thrombocytopenia and filter clotting was a problem for this patient when heparin-free CVVHDF was commenced. Danaparoid, a low molecular weight heparin indicated as an anticoagulant in patients prone to the development of HIT, was subsequently prescribed. Withdrawal of heparin during CVVHDF due to a clotting disorder also resulted in filter clotting for another patient.

13% of patients were receiving digoxin prior to treatment with CVVHDF. However, it was held during CVVHDF. The effect of digoxin is very much increased in renal impairment and it is avoided in ARF (86). Dose adjustment is required since 70% is renally excreted and pharmacokinetic equations can be used for this purpose. However, this approach was not seen in this audit. Instead, the antiarrhythmic drug amiodarone tended to be prescribed and was received by 27% of patients.

Noradrenaline was used in 82% of patients during CVVHDF, compared to 64% prior to starting CVVHDF, while adrenaline was prescribed for 64% of patients both prior to and during CVVHDF. Both adrenaline and noradrenaline were dosed according to response. Adrenaline is metabolised in the liver and other tissues by COMT and MAO enzymes, and is considered to be fairly safe for use during CRRT.

The use of dopamine and dobutamine as cardiac stimulants was found to be less extensive. Dopamine was used in 13% of patients before CVVHDF and in 6% of patients during CVVHDF. The use of dobutamine remained the same during CVVDF at 17%. The pharmacokinetics of dopamine and dobutamine were investigated in paediatric patients during CVVHDF by Freter et al (87). It was found that the clearance of dopamine and dobutamine by the haemofilter was negligible compared to total plasma clearance. Less than 1% of a dose was removed by the haemofilter in each case and so dosage adjustment of these catecholamines during CVVHDF is not required on the basis of this study.

Diuretics were commonly prescribed prior to commencing CVVHDF but their usage decreased considerably in patients undergoing CVVHDF. For example, frusemide was prescribed for fifteen patients before CVVHDF but only one patient received frusemide during CVVHDF. There are two potential reasons

for this trend; frusemide is a nephrotoxin and therefore should be avoided in acute renal failure in order to protect any residual renal function. Additionally, if a patient is in acute renal failure, the nephrons would not be responsive to the actions of frusemide. The relatively large proportion of patients receiving frusemide prior to requiring CVVHDF is significant considering its nephrotoxicity.

ACE inhibitors were among the admission drugs of 17% of patients. All antihypertensives are held during CVVHDF as hypotension becomes a problem during CRRT; however the potential nephrotoxicity of ACE inhibitors in causing renal insult may also be significant.

3.2.4 CNS Drugs: Pharmacokinetic Considerations for Sedation in Critically Ill Patients

CNS drugs such as benzodiazepines and opioids were commonly used to provide 'sedation' prior to the development of ARF. Morphine and midazolam were prescribed for 24% and 42% of patients respectively prior to commencing CVVHDF. There was a decrease in the consumption of CNS drugs during CVVHDF, as fentanyl and propofol were used for anaesthesia/sedation in preference to CNS drugs such as morphine and midazolam. The usage of fentanyl doubled to 97% during CVVHDF and usage of propofol increased from to 40% to 97%.

The aim of a sedative is to address the following but there is no ideal sedative that succeeds in meeting all of these criteria: hypnosis, anxiolysis, amnesia, anticonvulsant, be non-cumulative, be independent of renal or hepatic metabolic pathways, not produce respiratory or cardiovascular depression, be of modest cost, have a rapid onset and short offset time, have no prolonged effects on memory and have no long-term psychological effects.

Benzodiazepines were the most widely used sedatives in the ICU prior to starting CVVHDF. These agents provide hypnosis, amnesia and anxiolysis. They do not provide analgesia. Benzodiazepines are good anticonvulsants and also provide for some muscle relaxation. These drugs may be given po, pr or iv. Midazolam was the first line sedative used in the unit, in the absence of renal impairment and when a prolonged duration of action (>24 hours) was required. Thirty one of the thirty nine patients included in the audit received midazolam prior to commencing CVVHDF. Midazolam was administered at a dose of 1-5mg/hr for first 4-6 hours and then reduced to avoid accumulation. Dosage of midazolam was by titration and varied widely depending on factors such as prior exposure to benzodiazepines, age and physiological reserve, volume status, renal and hepatic dysfunction, co-administered drugs and history of alcohol consumption. However, no specific guidelines were in place for dosing relating to these factors and the reason for prescribing a given dose was not documented and the factors influencing decisions on dose had to be deduced from the medical notes.

Midazolam is an intravenous sedative commonly used during ventilation in critical illness. Advantages given for its use include its rapid onset of action, perceived short plasma half-life and ease of administration. Midazolam is metabolised via cytomchrome P450, 3A4 and 2B6 to a-hydroxymidazolam before undergoing glucuronidation to form a-hydroxy-midazolam-glucuronide, which is excreted in urine (88). In the critically ill, there may be extensive derangement of the pharmacokinetic profile of midazolam (89). Contributing factors are various but include the accumulation of the active a-hydroxy-midazolam glucuronide in renal failure and delayed hepatic extraction of the parent molecule in multiple organ failure. These complex kinetics may result in

prolonged sedation and increased length of mechanical ventilation and ICU stay. In addition, many patients with multiple organ dysfunction have frequently had episodes of hypotension, dysrhythmias and may have significant coagulopathy, all of which increase the probability of neurological damage. On stopping midazolam therapy, it is often difficult to establish whether a patient is 'slow-to-wake' as a result of midazolam oversedation or from events which have resulted in neurological damage. One study of 26 patients, designated as 'slow to wake', reported that midazolam was detected in the serum of 50% of patients after a median time from therapy cessation of 67 hours (90). As a consequence of these altered pharmacokinetics, the use of midazolam was avoided in ARF. Thus its frequency of use decreased from 79% in patients not receiving CVVHDF to 19% in patients on CVVHDF. According to ICU guidelines for sedation, midazolam should not be prescribed for patients with renal impairment; however, 19% of patients on CVVHDF received an intermittent dose of midazolam. Reasons for this breach of protocol were not given in the medical notes but it may be due to lack of awareness by on-call clinicians of the altered kinetics of midazolam in renal impairment. The practice of 'dosing to response' coupled with the drugs pharmacokinetic variability in critically ill patients means that its use cannot currently be used safely during ARF and CVVHDF therapy.

Propofol was the sedative of choice for patients with renal impairment or where short term sedation (<24 hours) was required. It was administered to 85% of patients receiving CVVHDF. It is a fast-acting, very effective anaesthetic agent with a rapid offset of action due to its rapid metabolism to inactive metabolites in the liver. These features make it very suitable for use in patients requiring short-term sedation or for anaesthesia for procedures in the

ICU. Although propofol has been shown to reduce time on mechanical ventilation compared with midazolam, it had not been shown to reduce time in ICU. Caution is required in hypovolaemic patients or those with impaired myocardial function as severe hypotension may result. Propofol is currently dosed according to response without regard to pharmacokinetic considerations. This is probably not the optimum approach as it can be difficult to estimate the dose required to achieve a particular level of sedation and this is variable among patients. Further pharmacokinetic investigation of this commonly used sedative would be useful.

Prior to starting CVVHDF, benzodiazepines were often combined with opioids (39% patients). This allowed lower doses of benzodiazepines to be used while capitalising on the opioid effects of respiratory and cough suppression to facilitate mechanical ventilation.

Opioids were found to be the mainstay of analgesia in the ICU. 24% of patients received morphine prior to starting CVVHDF and 97% of patients received fentanyl during CVVHDF therapy. If renal function was normal, morphine in the dosage range 1-5mg/hr was used in combination with midazolam for sedation/ analgesia. In the presence of renal impairment or when a shorter duration of action was required, morphine was substituted with fentanyl (50-150mcg/hr). Doses were titrated to effect by intermittent injection – the effect of analgesia was judged by patient response.

3.2.5 Gastrointestinal Drugs and Stress Ulcer Prophylaxis during CVVHDF

The most commonly prescribed gastrointestinal drugs were proton pump inhibitors and H2-antagonists, namely omeprazole and ranitidine. 80% of patients received omeprazole both prior to and during CVVHDF therapy. A

further 9% of patients initially received esomeprazole or lansoprazole and were subsequently switched to intravenous omeprazole. 6% of patients received ranitidine alone both prior to and during CVVHDF, while 3% of patients received ranitidine in combination with omeprazole during CVVHDF. Sucralfate was used in combination with one of these agents in 18% of patients. These were used for stress ulcer prophylaxis. Acute stress ulceration is associated with shock, sepsis, burns, multiple trauma, head injuries, spinal injuries and respiratory, renal and hepatic failure. There is some debate regarding the need for GI prophylaxis in critically ill patients and the choice of prophylactic treatment used.

The high level of omeprazole usage contrasts with data collected in the same unit in 2000, where only 30% of all patients receiving stress ulcer prophylaxis were prescribed omeprazole, while 70% received ranitidine. At this time, ranitidine was regarded as being sufficient protection against ulcers and was the GI prophylaxis agent of choice. The subsequent change in prescribing detected in this audit may reflect the results of a meta-analysis that showed that ranitidine did not confer any protection against stress ulcer in the intensive care patients (91). A problem of H2-receptor antagonists is the development of tachyphylaxis after the first day of administration, leading to reduction of effectiveness in acid suppression. Ranitidine is the agent of choice in AMNCH. Cimetidine is less potent and interacts with anticonvulsants, theophylline and warfarin may be problematic. Famotidine and nizatidine have no particular advantage over ranitidine. In AMNCH, the dose of ranitidine was usually reduced by 50% during CRRT, if creatinine clearance was less than 10ml/min to reduce the risk of confusion. All proton pump inhibitors (omeprazole, lansoprazole, pantoprazole and rabeprazole) can be given as oral medication.

Omeprazole and pantoprazole are also used in intravenous form. In two non-randomised studies, intravenous omeprazole has been shown to protect critically ill patients who required ventilation from the development of stress-related mucosal bleeding from the upper GI tract (92, 93). Omeprazole is not dose-reduced in renal impairment.

Prophylactic therapies to reduce the risk of upper GI bleeding include enteral nutrition, gastric acid suppression (e.g. omeprazole) and gastric mucosal coating (e.g. sucralphate). Prophylactic treatment aims for gastric alkalinization (gastric pH> 3.5), on the rationale that gastric acidity is the main cause of stress ulceration. The incidence of stress ulcerations appears to be lower with prophylactic gastric alkalinisation than with placebos, although an improvement in survival has not been shown. Gastric bacterial overgrowth and the associated nosocomial pneumonia has been a concern but not substantiated by existing data. On balance, the literature suggests that treatment should probably be reserved for at risk-patients and scoring systems to estimate the risk of stress ulcer bleeding have been proposed. There is little consensus among critical care experts in the choice of prophylactic treatment used.

Drugs given include antacids. Antacids given hourly via a nasogastric tube can maintain gastric alkalinization. Gastric pH monitoring is necessary. Bowel stasis and diarrhoea can be problems depending on the antacid used (and the minerals they contain). These were rarely used in AMNCH (n=1).

Sucralfate is a basic aluminium salt of sucrose octasulphate. It is effective in healing ulcers by increasing mucous secretion, mucosal blood flow and local prostaglandin production. These effects promote mucosal resistance against acid and pepsin (they are cytoprotective). As it does not alter gastric pH, gram-negative bacterial colonization is less likely. The incidence of nosocomial

pneumonia may be less with sucralfate than with antacids or H2-antagonists but this is debatable (91).

Lactulose was prescribed for 13% of patients for use as an osmotic laxative but also at a higher dose (30mls tds via the nasogastric tube) to improve encephalopathy in Acute Liver Failure. Anti-emetics were more commonly prescribed prior to than during CVVHDF. Prochlorperazine and cyclizine (in combination with morphine) were most commonly administered. Metoclopramide, domperidone and erythromycin were all used as prokinetic agents, metoclopramide being the most common choice.

3.3 Analysis of the use of Continuous Renal Replacement Therapy (CRRT) in ICU

CVVHDF is the form of continuous renal replacement used in AMNCH for the treatment of ARF. Its use is favoured over other forms of CRRT as it confers a number of advantages on the treatment of critically ill patients. This modality of renal replacement therapy is better tolerated in the hypotensive patient than other forms of renal replacement therapy, as it allows a more gradual control of the metabolic environment and allows ongoing titration of fluid balance. There are a number of CRRT factors that can affect drug pharmacokinetics in critically ill patients. The most prominent factor is the choice of filter. Three major mechanisms can be identified in the process of purifying uremic blood through a membrane:

(1) Diffusive transfer which follows a concentration gradient

(2) Convective flux which follows a pressure gradient

(3) Adsorption onto or within the membrane which depends on different types of chemical or physical interactions

The type of filter used in the hospital is an AN69 dialysis membrane (AN= acrylonitrile, M100 refers to the membrane size – there are four membrane sizes available but haemodiafiltration generally employs the M100 for most adult patients). The development of this type of membrane, which is highly permeable to water and middle molecular weight molecules, combined with the introduction of haemodiafiltration techniques, has meant that the current form of CRRT has much greater potential for drug clearance than more traditional forms of CRRT. As the sieving coefficient for a compound depends on the membrane used to generate the data, extrapolation of results from studies, where membranes other than the AN69 dialysis membrane are used, is difficult. CVVHDF uses a combination of convective and diffusive clearance, in contrast to haemodialysis and haemofiltration, which rely on diffusion and convection alone respectively. In addition, haemofiltration often uses lower ultrafiltration rates than CVVHDF. In order to understand the clinical impact of CVVHDF on drug pharmacokinetics, variations in effluent fluid flow rates must be considered. In this audit, this data was not always reliably recorded and in particular deviations from prescribed flow rates do not appear in the nursing or medical notes. Prospective studies that include data on any such variation and the impact of flow rates on drug clearance are required to improve understanding of drug clearance due to CVVHDF and so improve therapeutic outcomes.

Filter clotting was identified as being a problem for some patients in this study (n=8), particularly when dialysis was run 'heparin-free' (n=6). The impact of filter clotting and filter changes on drug clearance and the risk of reduced filter efficiency over time require consideration in these patients.

The PRISMA dialysis system is used for providing haemodiafiltration therapy in the AMNCH Intensive Care Unit. The manufacturers recommend replacing the circuit after 72 hours in use. This recommendation is based on the physical durability of the dialysis system rather than on the decrease in extraction efficiency of the haemofilters. After 72 hours, there is a risk of physical breakdown of tubing with the possibility of blood leaks. In the case of the 39 patients analysed in this audit, details of filter changes were recorded for 29 patients. Among this sample, filter changes occurred before 96 hours in all patients and before 72 hours in 22 patients. One study (94) investigated the long-term performance of haemofilters in continuous haemofiltration by measuring the filtering performance of six polyamide haemofilters with a running time exceeding 72 hours applied for continuous haemofiltration in ICU patients. The sieving coefficients for urea, creatinine and polyfructosan did not change with running time. The hydraulic permeability remained also unchanged. The investigators concluded that a daily routine change of polyamide haemofilters applied in continuous arteriovenous haemofiltration is not necessary within the first 72 hours of treatment, unless a major decrease in filtration rate occurs.

Transmembrane filter pressures, coagulation parameters and serum creatinine and urea values are viewed as the best markers of haemofilter efficiency and circuit function. Although, in vitro studies have sought to quantify filter efficiency over time, in terms of sieving coefficients, the belief is held that these does not always correlate with the in-vivo situation due to patient variability. However, in-vitro studies done under ideal conditions may provide a framework for forming guidelines, which could possibly be optimised for individual patients or certain patient groups. It might be more beneficial to look

at changes in sieving coefficients with changing transmembrane filter pressures than with time as duration of use does not seem to be the main limiting factor for maintaining circuit function. Comparison of the efficacy of different anticoagulants in prolonging circuit function is another consideration. Heparin is currently the agent of choice in AMNCH, but enoxaparin and danaparoid were also used among patients in this audit.

3.4 Audit Findings

The critical role of anti-infectives, in the treatment of ICU patients receiving CVVHDF, was highlighted in this audit. Sepsis led to the development of ARF in the majority of cases. However, the absence of an evidence-base and an associated lack of defined guidelines for the dosing of many antimicrobial drugs during CVVHDF were evident. A number of antimicrobials were identified as meriting further study, due to a number of factors, such as the frequency with which they were prescribed, the potential impact of subtherapeutic or toxic drug plasma concentrations on patients' outcomes, the absence of sufficient data on the drugs' pharmacokinetics in patients on CVVHDF and the likelihood that the drug would be significantly cleared by CVVHDF. The drugs selected were Ciprofloxacin, Amikacin, Gentamicin and Vancomycin. Clearances are increased for drugs that have a high fraction of renal elimination. The ideal drug to be removed by continuous renal replacement therapy that requires a dose adjustment has: a low protein binding, a low volume of distribution, and a low non-renal clearance. Vancomycin, Amikacin and Gentamicin particularly meet these criteria making them good candidates for CVVHDF clearance, and in addition are frequently prescribed for serious infection in this patient group where therapeutic efficacy is critical.

Ciprofloxacin will be considered as an example of a commonly prescribed anti-infective, with a larger Vd, whose major but not only route of elimination is the renal route.

Although, antimicrobial therapy efficacy is critical in terms of positive patient outcomes, there is sparse clinical data on the pharmacokinetics of commonly used antimicrobials during CVVHDF under the conditions used in this Hospital. The variability of dosing schedules of Ciprofloxacin and Vancomycin used during CVVHDF observed in this audit, together with the failure to adjust dosage regimens for certain drugs (e.g. Aminoglycosides) to account for CVVHDF clearance indicate that further pharmacokinetic studies of these drugs during CVVHDF therapy are necessary.

Duration of filter use and the efficiency of filters over time may have role in influencing drug pharmacokinetics during CVVHDF, which has not been satisfactorily assessed, and these issues need to be investigated in prospective studies. The ultrafiltration rates and dialysis flow rates, filter membranes Patient factors, CVVHDF system factors and drug factors will all impact on drug pharmacokinetics. These factors will influence the design of prospective pharmacokinetic studies.

Chapter 4: An Evaluation of Vancomycin Pharmacokinetics during Critical Illness and Treatment with CVVHDF.

4.1 Introduction

4.1.1 Vancomycin: Mechanism of Action and Antimicrobial Activity.

Glycopeptides are bactericidal antibiotics which are active against Gram positive species and act by inhibiting peptidoglycan synthesis. Notwithstanding variations in bacterial epidemiology in different countries and different Intensive Care Units, there has been a progressive increase in the incidence of infection due to Gram-positive aerobic bacteria over the last 15 years. In the audit carried out in this ICU, staphylococcus aureus was the etiologic agent most frequently responsible for infections in the ICU; Staphylococcua aureus (S. aureus), coagulase negative Staphylococcus and Enterococcus were responsible for more than 60% of infections. More recent data indicate an increase in the incidence of methicillin-resistance S. aureus (M.R.S.A.). The high percentage of multi-resistance compels us to reconsider therapy relative to the choice of antibiotic, dosing and monitoring.

Vancomycin is an effective antibiotic for a variety of serious gram-positive infections. However, because of emerging resistance in enterococci and staphylococci and the emerging threat of spread of vancomycin-resistant genes to other gram-positive organisms, the judicious use of vancomycin should be promoted.

Vancomycin is a complex glycopeptide with a molecular weight of approximately 1,500 Daltons. It exerts its primary bactericidal effect by inhibiting the biosynthesis of the major structural polymer of the baterial cell wall, peptidoglycan (95). Vancomycin inhibits vital peptidoglycan polymerase and transpeptidation reactions which subsequently cause cell lysis. It inhibits

the second stage of synthesis of peptidoglycan at a site earlier than the site of action of penicillin and thus no cross reactivity occurs. Vancomycin affects the permeability of cytoplasmic membranes and may impair synthesis of RNA. For most gram-positive organisms, vancomycin is bactericidal, except for enterococci (96). For Enterococcus faecalis it is bacteriostatic. Its relatively large size prevents it crossing the outer cell wall of gram-negative bacteria, thus it is not active against these organisms.

The antibacterial spectrum of vancomycin is largely limited to aerobic and anaerobic gram-positive organisms. It is highly effective against gram-positive cocci, such as S. aureus and coagulase negative staphylococci. All strains of Streptococci are susceptible and vancomycin has excellent activity against Strep. pneumoniae, including penicillin resistant strains (95, 98). It is synergistic with gentamicin against most strains of S.aureus and enterococci (99, 100). There has been resurgence in the use of vancomycin because of an increased prevalence of MRSA. Vancomycin is also effective against anaerobes, diptheroids and Clostridium spp., including Clostridium difficile. Vancomycin is bactericidal at clinically achievable concentrations (Minimum Bactericidal Concentration (MBC) to Minimum Inhibitory Concentration (MIC) < 4) against most strains of S. aureus, coagulase negative staphylococci, corynebacteria, gram positive Bacillus species, β-hemolytic streptococci, viridans streptococci, anaerobic cocci, and clostridia (95,97,98). It is bacteriostatic against most strains of enterococci, and for Enterococcus faecium and E. faecalis, concentrations of 100mg/L or greater are required for a bactericidal effect (98). Gram negative bacteria are generally resistant except for occasional isolates of Neisseria gonorrhoeae (98, 101). Although vancomycin has been successfully used to treat infections due to

Flacobacterium meningosepticum, these organisms are usually resistant in vitro (98). All other gram-negative bacteria including anaerobes are resistant (101). Mycobacteria and fungi are vancomycin resistant. The MIC of vancomycin for most strains of S. aureus (methicillin-sensitive) is in the range 0.25-2.0 mg/L, for MRSA is 0.4-2.0 mg/L, for coagulase-negative staphylococci is 0.39 -3.12 mg/L (101).

Acquired vancomycin-resistance, most commonly involves Enterococcus species, but has also been described in coagulase-negative staphylococci. Almost all resistant infections to enterococci have been nosocomially acquired. Affected patients have usually been hospitalised for long periods of time, have received multiple courses of antibiotics (including third-generation cephalosporins or vancomycin) and usually suffer from other serious underlying medical or surgical conditions (101). For example, there have been literature reports of clusters of infected patients in specific hospital areas including the ICU, but also the renal unit and oncology wards (101). When tolerance has been demonstrated, most clinicians add a second antibiotic to the regimen. Vancomycin in combination with gentamicin is usually recommended for treatment of enterococcal infections.

4.1.2 Clinical Pharmacokinetics

Vancomycin is poorly absorbed from the gastrointestinal tract and is administered orally for the treatment of Clostridium difficile induced antibiotic-associated pseudomembranous colitis. Its oral bioavailability is less than 10% (102). However, there have been reports of detectable serum concentrations in patients with severe renal impairment who had been receiving oral vancomycin for the treatment of pseudomembranous colitis and

a suggestion that inflammation of the gut wall increases vancomycin bioavailability (103, 104, 105).

When vancomycin is used to treat systemic infections, it is usually given intravenously at an infusion rate of not more than 10mg/min. It should not be administered intramuscularly because of the possibility of tissue necrosis and severe pain. It may be given intraperitoneally for patients with peritonitis receiving peritoneal dialysis. Systemic absorption of vancomycin after intraperitoneal administration is 54 to 65% of a given dose in 6 hours.

The Vd of vancomycin is highly variable, ranging from 0.5L/kg to 1.0L/kg in non-obese patients with normal renal function (106, 107). In clinical practice, an average Vd of 0.7L/kg is often used. The Vd can be affected by age, gender, body weight, but fluid balance is less of an issue than for the aminoglycosides. Rushing (108) et al has suggested a method for estimating Vd for vancomycin, which incorporates patient's TBW and age.

Vd (L/kg) = 0.17(age in years) + (0.22)(TBW in kg) + 15 (Equation 4.1.1)

Vancomycin is not highly protein bound – a range for protein binding of 30-55% has been reported for healthy volunteers (109,110,111).

Vancomycin is not metabolized to any great extent. 80-90% of the intravenously administered dose can be recovered unchanged in the urine in 24 hours (112). Only small amounts are recovered in bile and dosage adjustment is not usually required for patients with liver failure (109).

Vancomycin is primarily eliminated by the renal route. Vancomycin is mainly excreted by glomerular filtration and so dosage adjustment is required for patients with renal dysfunction. Creatinine clearance may be used to approximate vancomycin clearance but is not equivalent. In practice, the following equation is often used to estimate a patient's vancomycin clearance:

Clvanc = 0.65 x Clcr x TBW (Kg), (Equation 4.1.2)

where TBW is total body weight. Vancomycin clearance correlates better with total body weight in obese patients.

Vancomycin half-life in patients with normal renal function is 5-10 hours but in patients with severe renal impairment, the half-life is prolonged (17-34 fold increase in the half-life) and may approach 7 days (113, 114, and 115). Disease states and conditions that affect renal function will affect vancomycin clearance. As vancomycin is primarily eliminated by glomerular filtration, any change in renal function will impact on its clearance. A number of studies (109, 113, 115, 116) have characterized the relationship between the degree of renal impairment and the degree of decline in vancomycin TBC. Patients with acute renal failure appear to have substantial compensatory nonrenal clearance initially, but as the duration of renal failure increases, the nonrenal clearance decreases and approaches that observed in patients with chronic renal failure (117). Extensive burns can cause significant changes in vancomycin disposition, resulting in a decreased half-life (110, 118, 119). Intravenous drug abusers (110) and critically ill patients (120) also have considerably increased vancomycin clearance. Obese patients also have increased vancomycin clearance due to kidney hypertrophy (106,107,121,122).

4.1.3 Pharmacokinetic models for Vancomycin

The pharmacokinetics of vancomycin (k_{el}, $t_{1/2\alpha}$, $t_{1/2\beta}$, V_1, Vd_{ext}, TBC) are best described using a two- or three- compartment model. However, in clinical situation, a one-compartment model has been found adequate to determine effective dosage regimens. The use of a one-compartment model, requiring fewer serum samples offers benefit in terms of patient comfort, nursing time and financial cost. Vancomycin serum concentrations drop rapidly during the α

or distribution phase, because of distribution of drug from blood to tissue. Approximately 30-60 minutes after the end of the infusion, during the β or elimination phase, serum concentrations of vancomycin drop more slowly and the elimination rate constant for this portion of the concentration-time curve varies with renal function.

A review of pharmacokinetic optimisation of vancomycin therapy by Leader et al (123) concluded that a one-compartment model is adequate for vancomycin dosage adjustments if C_{pmax} values are sampled after the distributive phase. Similarly, Pou et al (124) used a one-compartment model to investigate changes in vancomycin pharmacokinetics during treatment, commenting that in a clinical context, that it is difficult to justify the numerous serum samples necessary for a two-compartment model. Pryka et al (125) compared the performance of one- and two- compartment population models for predicting C_{pmax} and C_{pmin} values of vanocmycin and no significant difference in the estimated pharmacokinetic parameters was seen when steady-state concentrations were used. They defined C_{pmax} (peak) values as concentrations sampled one hour after a 1-hour infusion and C_{pmin} (trough) as 30 minutes before the dose. Rybak and Boike (126) observed no significant differences in pharmacokinetic parameters calculated using a one-compartment model when serum concentrations were drawn 1, 2 or 3 hours after the end of a 1-hour infusion.

4.1.4 Therapeutic Drug Monitoring of Vancomycin

Knowledge of the desired therapeutic range and pharmacokinetic parameters of vancomycin for an individual patient allow the selection of doses and dosing intervals that meet the specific needs of the critically ill patient. The use of different infusion times, altered renal function, age and concomitant disease states can cause variability in vancomycin disposition and in serum concentrations due to patient inter-variability. These factors must be considered in conjunction with the specific site of infection, the suspected pathogen and the clinical status of the patient, when designing a suitable dosage regimen. Dosing nomograms for vancomycin are available, for example that included in the Vancocin product SPC, however their use for critically ill patients is inadvisable due to the level of pharmacokinetic variability among these patients. Vancomycin nomograms are based on renal function alone and in critically ill patients where it is difficult to assess rapidly changing renal function may not be appropriate. A minimum of two carefully-timed serum concentrations within a single dosage interval are required to obtain estimates of k and Vd for an individual patient. Thus, monitoring of both peak and trough concentrations (or any two timed concentrations after the distribution phase is complete) is essential for dosage optimization in patients such as the critically ill where it is difficult to predict pharmacokinetic parameters with confidence. The first step in designing an appropriate dosing regimen for a patient is to obtain estimates of k and Vd ($t_{1/2}$ and Cl). The next step is to calculate the vancomycin maintenance dose, dosing interval and a loading dose if necessary.

4.1.5 Pharmacodynamic properties

The pharmacodynamic properties of vancomycin are time-dependent killing and minimal post antibiotic effect. At therapeutic concentrations, vancomycin appears to exert a concentration-independent bactericidal effect; as long as vancomycin concentrations are 4-5 times the MIC (127), vancomycin displays concentration independent killing (128, 129).

Duffull et al (129) used a pharmacodynamic in vitro model to study four different vancomycin dosage regimens against S. aureus and concluded that the optimal dosing method for vancomycin may be one that achieves the lowest area under the curve while maintaining concentrations greater than the minimum bactericidal concentration.

Knudsen et al (130) studied vancomycin pharmacodynamics in a mouse peritonitis model with S.aureus and Streptococcus pneumoniae as the infecting organisms. They reported a statistically significant better survival when the dose required to achieve ED_{50} was administered as a single dose compared to two divided doses. Ahmed et al (127) reported a maximal killing rate at vancomycin concentrations four times the MBC in rabbits with experimental pneumococcal meningitis. Sorrell et al (131) found the MBC to MIC ratio to be predictive of successful response to vancomycin in a study of patients with S. aureus associated bacteremia. A retrospective study (132) found that patients with MRSA-infected pneumonia or bacteremia had superior outcomes if peak concentrations were at least 25mg/L. They concluded that it is important to obtain effective drug concentrations at the infection site irrespective of whether the antibiotic has concentration-dependent or time-dependent killing. Another retrospective investigation (133) of patients with S. aureus associated lower respiratory tract infections found the 24-hour AUC to

MIC ratio to be predictive of outcome in the subset of patients with MRSA infections.

Based on this review of the literature, the aim of therapy should be to maintain vancomycin concentrations four to five times above the MIC of susceptible bacteria for the duration of the dosage interval. Because the average vancomycin MIC values for S. aureus and S. epidermidis are 1 to 2 mg/L, if we want to maintain serum concentrations four to five times above the MIC, trough levels of at least 5 or 10mg/L with MIC values of 1 or 2mg/L respectively, appear reasonable. Thus, Hospital practice of using trough concentration ranges of 5-12mg/L is in line with literature recommendations. However, MIC values of up to 4mg/L have been reported for susceptible microorganisms and where this is the case, higher trough concentrations should be targeted.

4.1.6 Adverse effects

The major adverse effects associated with vancomcyin are nephrotoxicity and ototoxicity. The incidence of these effects is quite small – approximately 5% for nephrotoxicity (129,130) and less than 2% for ototoxicity. The original formulations of vancomycin contained impurities now thought to have contributed to the early cases of nephrotoxicity and current preparation are likely to have less potential for toxicity. The incidence of nephrotoxicity is higher when vancomycin is coadministered with an aminoglycoside, with a reported range of 22-35% (133, 134, 135, 136). Certain patients, for example those with neutropenia, increase age, liver disease or concurrent amphotericin B therapy, may have an increased risk of developing nephrotoxicity (136). Investigations on vancomcyin-induced ototoxicity have raised the possibility that ototoxicity may be related to excessively high serum levels such as

80mg/L or greater, and recommendations were set that levels greater than 40-50mg/L should be avoided to prevent ototoxicity (133,137). Nonconcentration related toxicities have been reported with vancomycin. Rapid intravenous infusion of vancomycin, greater than 10mg/min, may result in a histamine-like reaction characterised by flushing, local pruritus, erythema of the neck and upper torso, tachycardia or hypotension. This hypersensitivity reaction is referred to as 'red man syndrome'. It usually occurs soon after the infusion is started but can be delayed (114,138).

4.1.7 Effects of Dialysis and CRRT on Vancomycin Disposition

In patients with ESRD receiving dialysis and concurrent vancomycin therapy, the elimination of the drug during the dialysis procedure must be considered. Very little vancomycin is cleared by standard intermittent haemodialysis or peritoneal dialysis (113, 139, 140). However, high flux methods of haemodialysis and Continuous Renal Replacement Therapies may remove substantial amounts of the drug.

Dosing recommendations for vancomycin during critical illness vary. In intensive care patients without renal impairment, doses used range from 15mg/kg (1050mg for 70kg patient) every 24 hours to 2g every 12 hours (137). In critically ill patients with renal insufficiency, dosage reduction is recommended and the dosage interval ranges from 24 hours to 240 hours (138). During conventional dialytic therapies, vancomycin is administered once every 7-10 days, since the half-life is of this order and this is the equivalent of dosing at intervals of the half-life, to avoid accumulation. Vancomycin is not significantly cleared by intermittent haemodialysis or peritoneal dialysis and so the half-life is similar to that seen in undialysed patients with severe renal impairment (139,140). A vancomycin clearance of only 3.8L/ day has been

reported for conventional dialysis (141).

Previous studies (142, 143, 63) investigated vancomycin pharmacokinetics in patients receiving earlier forms of continuous renal support, such as CVVHF and CAVH. A prospective study of vancomycin clearance in two critically ill patients, treated with CVVHF, recommended a loading dose of 15-20 mg/ kg followed after 24 hours by 250 mg to 500 mg twice daily (142). Another study advised a vancomycin dosage regimen of 850-1050 mg/day in patients receiving CVVHF. However, the patients in the study were end-stage renal failure patients and were not in a critical condition (63). A recommendation of 1000 mg vancomycin every 48 hours has been suggested as an appropriate dose for use during CAVHD (143). As CVVHDF achieves higher drug clearances than other forms of renal replacement therapy (65, 72, 74, 144), its increasing use requires that the impact of continuous renal replacement (CRRT) therapy on vancomycin pharmacokinetics be reassessed. One prospective study with three patients advised that 7.5 mg /kg of vancomycin should be given intravenously every 12 hours to critically ill patients receiving CVVHDF (145). Small sample size, the variation in dosing recommendations reported, as well as the difficulty in extrapolating data obtained from stable patients or those receiving CVVH/CAVHD to critically ill patients treated with CVVHDF makes further investigation of vancomycin pharmacokinetics during CVVHDF desirable.

4.2 Retrospective Pharmacokinetic Evaluation of Vancomycin in Critically Ill Patients during CVVHDF therapy.

4.2.1 Patient Demographics and Clinical Characteristics

The patient population was described by age, sex, serum creatinine, Acute Physiology and Chronic Health Evaluation (APACHE) Π score, maximum Sequential Organ Failure Assessment (SOFA) score, admitting diagnosis and microbiological infection. Weight measurements were unavailable due to the clinical status of these patients, who were unconscious or sedated. Of the 32 patients considered, there was adequate data available for sixteen patients for their inclusion in the analysis. Patients whose CVVHDF therapy was interrupted while receiving vancomycin (n=10), or where the required minimum of two serum drug concentrations for a dosage interval were absent (n=6), were not included in the study. Seven women and nine men successively treated with vancomycin during CVVHDF therapy, ages 40-85 years (mean 60.3 +/- 14.1 years), were examined.

Seven patients had diagnosed pre-existing renal impairment prior to this Hospital admission. All patients had acute renal impairment. Nine patients had concurrent hepatic impairment. Oedema was recorded in four patients. Four patients (25%) were treated empirically for suspected sepsis. Coagulase negative staphylococci was the most common pathogen isolated (n=9). Five patients tested positive for MRSA. Four patients had concurrent documented gram-negative infection. These included Klebsiella, E. coli and Pseudomonas aeruginosa.

The mean APACHE Π score was 23.3 +/- 6.9. The APACHE (Acute Physiology and Chronic Health Evaluation) is a system for classifying patients in the intensive care unit. Patients are evaluated by physiologic scores and

evaluation of chronic health status. Physiological scores correlate with severity of illness. Results of the evaluation can be used to estimate the mortality rate for patients in the ICU and during the hospitalisation. The physiological data is evaluated during the first 32 hours after admission to the ICU. Each variable is assigned a value of 0 to 4, based on significance of deviation from normal, with more severe deviations given higher values. Probability of Death in Hospital based on APACHE score is 70% with an APACHE score of greater than 31 and 56.4% with a score of 26-31, 28.6% with a score of 21-25and 16.4% with a score of 16-20. The highest APACHE score was observed for a patient with acute hepatic and renal failure, cardiovascular instability and sepsis, with systemic MRSA infection.

The SOFA score is a scoring system to determine the extent of a person's organ function or rate of failure. Initial SOFA scores were calculated in this study. The highest SOFA score among this sample was 13, in a patient with renal, hepatic and respiratory failure and the lowest was 3 in a previously healthy patient admitted following a drug overdose. In a study of SOFA scores, initial and highest scores of more than 11 or mean scores of more than 5 corresponded to mortality of more than 80%. Of the five patients with an initial SOFA score equal to or in excess of 11, only one survived, which corresponds to the finding of 80% mortality with an initial SOFA score of more than 11, reported by Ferreira et al (146).

The mean duration of CVVHDF therapy was 11.9 +/- 7.4 days. The reasons for starting CVVHDF therapy included acute renal failure and sepsis, fluid overload, metabolic acidosis or End Stage Renal Failure (ESRF), where haemodialysis was not tolerated. The mean estimated creatinine clearance among these patients prior to commencing CVVHDF therapy was

5.188ml/min, which is approximately 0.3L/hr. This can be used as a crude approximation of vancomycin clearance in these patients prior to CVVHDF. A summary of clinical and demographic data are presented in Table 4.2.1

Table 4.2.1: Patient Demographics and Clinical Characteristics

ID	Sex	Age	Diagnosis	Infective Diagnosis	APACHE II score[1]	SOFA Score[2]	Sr Cr[3]	Cr Cl[4]	Duration CVVHDF (days)
1	M	82	Kidney cyst, Acute renal failure (ARF), Pulmonary embolism	Klebsiella (blood) Diphtheroids, coagulase negative staphylococci	26	6	141	5	11
2	F	54	ESRF, heart failure, pulmonary oedema	Coagulase negative staphylococci (blood)	21	9	387	2	3
3	M	56	Multiple myeloma, acute and chronic renal failure, acidosis, oedema, Coagulopathy	Empiric cover for suspected sepsis	28	10	156	6	17
4	M	40	Pancreatitis, ARF, ATN, sepsis, SIRS, acidosis, oedema	Empiric cover for suspected sepsis	30	11	145	8	15
5	M	49	Oesophageal varices Pancreatitis, sepsis, acidosis, ARDS, SIRS, coagulopathy	Coagulase negative staphylococci (blood) Gram negative bacillus (sputum, peritoneum)	32	12	115	9	18
6	F	71	Respiratory failure, MODS, oedema, anuric ARF, liver failure	Coagulase negative staphylococci (blood)	29	13	108	6	5
7	F	54	ARF 2y rhabdomyolysis, acute hepatic impairment, acidosis, oedema	Empiric cover for suspected sepsis	25	10	755	2	15
8	F	75	Post op (laparotomy, resection) sepsis	Coagulase negative staphylococci (blood)	11	3	207	3	9
9	F	61	MODS 2y necrotic	Coagulase negative	19	7	188	5	34

			pancreatitis	staphylococci					
10	F	43	Acute on chronic renal failure, alcoholic liver disease	Empiric cover for suspected sepsis	22	8	580	2	9
11	M	53	Acute hepatic failure secondary to renal failure secondary to hypoperfusion Acute on chronic renal failure and ischaemic ATN, anuric	MRSA	34	11	121	8	6
12	F	79	Acute on chronic renal insufficiency, hypertension, Atrial fibrillation., acidosis	Coagulase negative staphylococci	19	7	318	3	8
13	M	62	Infective exacerbated Type 2 COAD, Hypotension, Acidosis, Impaired liver function, ARF, oedema	MRSA, Escherichia coli, Klebsiella pneumoniae, Candida albicans.	27	12	205	4	6
14	M	46	Drug Overdose	Coagulase negative staphylocci, MRSA	11	3	87	9	11
15	M	54	Bowel obstruction, sepsis. oedema	Coagulase negative staphylococci MRSA	17	4	448	2	9
16	M	85	Acute on chronic renal failure, Hypertension, Lower RTI	MRSA, Klebsiella.	21	8	227	9	14

[1] Initial/Admission score
[2] Initial/Admission score
[3] value on day 1 of CVVHDF therapy; units = μmol/L
[4] value prior to commencing CVVHDF therapy; units = ml/min. Estimated using Jelliffe and Jelliffe method (42).

4.2.2 Pharmacokinetic Analysis and Clinical Observations

Pharmacokinetic parameters were estimated from vancomycin serum concentration-time data. Doses administered were 0.75g, 1g and 1.5g. The dosage intervals used ranged from 12 to 53 hours. Individual patient pharmacokinetic parameters for vancomycin during CVVHDF therapy were estimated on the basis of a one-compartment model, using the method of Sawchuk and Zaske, as outlined in Chapter 2. Pharmacokinetic parameters were estimated from serum concentration data, with careful consultation of drug administration records (dose administered, time administered, duration of the infusion). Variations in peak concentrations may be in part attributed to variations in sampling times. When a blood sample was taken at a time point that differed from the 'designated time' for obtaining a peak concentration, but was still in the timeframe considered appropriate for sampling, which was defined as at least 1 hour after the infusion was complete, and the exact time of blood sampling was recorded, the serum concentration at this time point was included in the analysis.

Dosing schedule 1: 1g Vancomycin every 24 hours

The most common dosing schedule was 1g vancomycin every 24 hours. As the dose for patients with normal renal function is 1g twice daily; this dosing schedule represents an extension of the dosage interval, on the basis of patients' renal impairment. Figure 4.1.1 displays a semi-log plot of vancomycin peak and trough serum concentration versus time for patients treated with this dosing regimen.

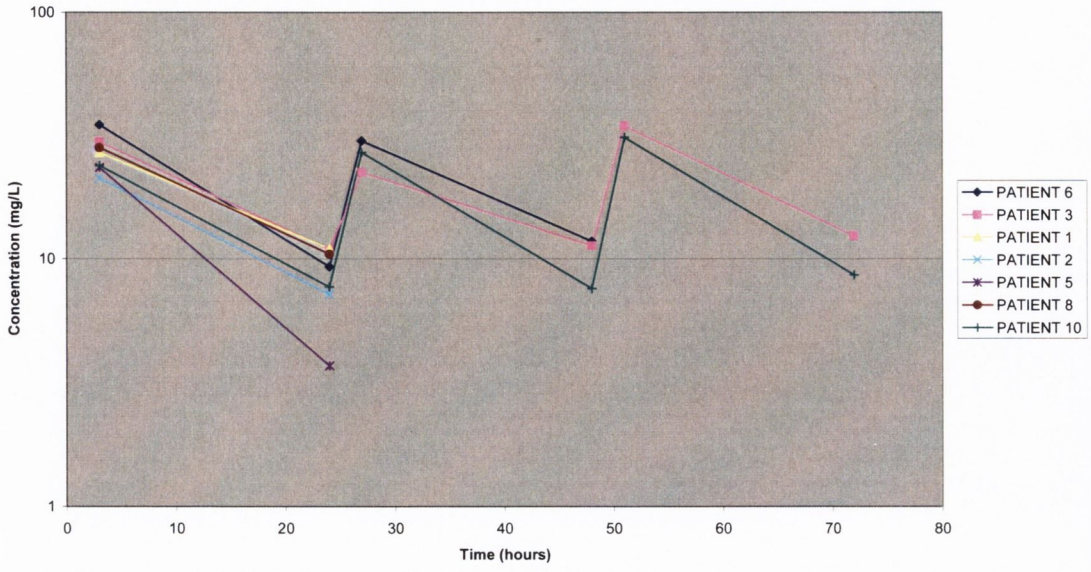


Figure 4.2.1: Semi-log plot of Vancomycin serum concentration-time data for seven patients administered Vancomycin 1g every 24 hours.

The mean half-life ($t_{1/2}$) and mean elimination rate constant (k) were 16.1 hours and 0.046 hr^{-1} respectively. The mean half-life was less than the dosage interval and accumulation did not occur. The mean Total Body Clearance (TBC) was 2.27 L/hr and the range of estimates of Vd was 36.1 L – 84.1 L.

Dosing Schedule 2: 1.5g every 24 hours

Vancomycin 1.5g was administered to three patients (patients 4, 7 and 15), while the dosage interval was varied from 16 to 30 hours. For two further patients (patients 13 and 16), 1.5g Vancomycin was administered every 24 hours for the duration of therapy.

For patient 4, the range of elimination rate constants (k) was 0.030 hr^{-1} to 0.057 hr^{-1}. In the case of this patient, the half-life remained consistent (mean 16.5 hours), with the notable exception of the second dosage interval, where the elimination rate constant estimated was significantly lower (0.030 hr^{-1}) than for all other pharmacokinetic profiles in this patient. A reduction in the

ultrafiltration rate, from 2000ml/min to 1600ml/minute may partially explain the extended half-life during this dosage interval. As the dosage intervals used exceeded the estimated half-life, vancomycin doses of 1.5g did not result in accumulation. Similarly, in patient 7, a dosing schedule of 1.5g every 24 hours resulted in target trough concentrations for four dosage intervals, where the mean half-life estimate was 15.4 hours. A decreased elimination rate constant and an increased apparent volume of distribution were observed at the fifth dosage interval, which coincided with an increase in the patient's daily serum urea and creatinine measurements. This patient was anuric throughout CVVHDF therapy. For patients 13 and 16, the dosing schedule of 1.5g maintained target therapeutic concentrations, with the exception of one trough concentration, which slightly exceeded the general target range. For patient 16, the C_{pmax} concentrations ranged from 32.7 to 38.1 mg/L and the C_{pmin} concentrations ranged from 9.5-13.5 mg/L. The mean half-life was 15.3 +/- 3.4 hours and the mean clearance was 2.68 +/- 0.08 L/hr. The ultrafiltrate rate and dialysis fluid flow rates were 2L/hr, which should produce a total effluent flow rate of 4L/hr. For patient 13, treated with a similar dosing regimen, the C_{pmax} concentrations ranged from 25.4 mg/L to 27.5 mg/L. The C_{pmin} concentrations ranged from 10.3 – 11.9 mg/L. The mean half-life was 18.8 +/- 1.3 hours and the mean clearance was 2.1 +/- 0.1 L/hr. The mean Vd was 58.8 +/- 7.7 L. The ultrafiltrate and dialysate flow rates were 2L/hr and 1L/hr respectively.

Dosing schedule 3: Dosage increase from 1g to 1.5g every 24 hours

The impact of a dosage increase from 1g to 1.5g vancomycin was observed in two patients. In the case of patient 3, the patient's clinical status deteriorated between the third and fourth dose of vancomycin during CVVHDF therapy.

The fourth dose was subsequently increased to 1.5g vancomycin, while the dosage interval of 24 hours was maintained. At this point, the patient had documented oedema and the increased volume of distribution observed may be due to increased extravascular fluid. Resultant trough concentrations exceeded the target range of 5-12mg/L, but higher trough concentrations may have been considered appropriate for this patient.

Dosage adjustment for patient 5 also involved increasing the dose from 1g to 1.5g vancomycin. The mean half-life estimate for this patient was 14 hours. The half-life was significantly extended during the second dosage interval – a reduction in filter efficiency may have related to coagulopathy in this highly unstable patient.

Dosing schedule 4: 0.75g every 24 hours

The lowest dose used was 0.75g, which was administered to one patient (patient no. 9) at varying dosage intervals. A trough concentration below 5mg/L was obtained (3.9mg/L), thirty hours after the administration of a 0.75g dose. The minimum inhibitory concentration for most strains of staphylococcus is below 5mg/L; therefore trough concentrations should be maintained in the range of 5-15mg/L. The dose was subsequently increased to 1.5g, resulting in a trough of 15.7 mg/L after 18 hours.

Individual patient estimates of pharmacokinetic parameters are given in Table 4.2.2.

Table 4.2.2: Estimates of individual patient pharmacokinetic parameters for vancomycin during CVVHDF therapy, derived from vancomycin C_{pmax} and C_{pmin} serum concentrations.

ID	UF Rate (ml/hr)	Dose (g)	Dosage Interval (hours)	Cpmax (mg/L)	Cpmin (mg/L)	k (hr^{-1})	$T_{1/2}$ (hours)	Clearance (L/hr)	Vd (L)
1	2000	1.0	24	26.9	11.0	**0.036**	**19.25**	**2.169**	**60.26**
2	2000	1.0	24	21.2	7.2	0.039	17.77	2.488	63.80
	2000	1.0	12	20.3	8.9	0.038	18.24	3.063	80.60
	2000	1.0	12	26.6	16.2	0.041	16.90	3.655	89.15
	2000	1.0	12	26.5	17.3	0.036	19.25	3.519	97.77
x						**0.039**	**18.04**	**3.181**	**82.83**
3	2000	1.0	24	29.7	10.9	0.036	19.25	1.849	51.35
	1950	1.0	24	22.4	11.3	0.027	25.67	2.272	84.14
	2000	1.0	24	34.5	12.4	0.042	16.50	0.831	41.73
	2000	1.5	24	30.9	16.0	0.027	25.67	2.447	90.62
	2000	1.5	24	27.4	13.6	0.029	23.90	2.847	98.18
x						**0.032**	**22.19**	**2.049**	**73.36**
4	2000	1.5	16	34.7	13.8	0.057	12.16	3.431	60.20
	1600	1.5	30	32.1	12.5	0.030	23.10	2.107	70.24
	2000	1.5	24	31.7	12.2	0.040	17.33	2.904	72.60
	2000	1.5	24	33.2	11.5	0.042	16.50	2.559	61.90
	2000	1.5	24	35.8	11.5	0.047	14.74	2.601	55.35
	2000	1.5	26	36.1	12.2	0.042	16.50	2.389	56.88
	2000	1.5	26	35.2	11.0	0.045	15.40	2.507	55.71
x						**0.043**	**16.53**	**2.648**	**61.84**
5	2000	1.0	24	23.4	3.7	0.076	9.12	3.567	46.94
	2000	1.5	36	26.0	12.4	0.021	33.69	2.156	102.7
	2000	1.0	12	29.7	13.4	0.066	10.50	3.519	53.32
	2000	1.5	12	30.1	12.0	0.076	9.12	5.144	67.69
	2000	1.5	14	31.7	16.1	0.048	14.43	3.549	73.93
	2000	1.5	14	32.0	13.7	0.061	11.36	4.180	68.53
x						**0.058**	**14.70**	**3.658**	**69.68**
6	2000	1.0	24	34.9	9.3	0.055	12.60	1.989	36.18
	1900	1.0	24	30.0	11.8	0.039	17.77	2.007	51.45
x						**0.047**	**15.18**	**1.998**	**43.67**
7	2000	1.5	24	30.7	9.4	0.049	14.14	3.090	63.07
	2000	1.5	24	31.4	10.3	0.046	15.07	2.970	64.57
	2000	1.5	24	34.3	11.5	0.045	15.40	2.625	58.34
	2000	1.5	24	31.7	11.8	0.041	16.90	2.716	66.24
	2000	1.5	24	28.1	14.4	0.028	24.75	2.765	98.75
x						**0.042**	**17.25**	**2.833**	**70.19**
8	2000	1.0	24	28.2	10.5	**0.041**	**16.90**	**2.143**	**52.27**
9	1900	0.75	36	18.9	5.9	0.030	23.10	1.683	56.11
	1900	0.75	30	19.0	5.0	0.045	15.40	2.299	51.10
x						**0.038**	**19.25**	**1.991**	**53.61**
10	2000	1.0	15	34.6	11.6	0.070	9.90	2.713	38.75
	2000	1.0	48	40.8	3.9	0.049	14.17	1.237	25.25
	2000	1.0	24	23.8	7.7	0.057	12.16	3.208	56.28
	2000	1.0	24	26.9	7.6	0.052	13.33	2.498	48.04
	2000	1.0	24	31.0	8.6	0.052	13.08	2.193	41.37
x						**0.056**	**12.52**	**2.370**	**41.94**
11	1900	1.0	27	25.0	9.3	0.037	18.92	2.429	49.97
	1900	1.0	24	32.2	13.0	0.043	16.12	2.107	49.01
x						**0.040**	**17.52**	**2.268**	**49.49**
12	1000	1.0	24	20.5	7.6	**0.040**	**17.33**	**1.420**	**35.53**
13	2000	1.5	24	27.2	10.3	0.040	17.33	2.130	53.24

	2000	1.5	24	25.4	10.6	0.036	19.25	2.218	55.46
	2000	1.5	24	27.5	11.9	0.035	19.80	2.027	67.55
x						**0.037**	**18.73**	**2.125**	**58.75**
	*	1.5	24	24.6	16.1	0.018	39.23	0.897	49.86
14	2000	1.0	24	22.5	6.8	0.07	9.90	3.476	49.66
15	2000	1.5	36	25.7	6.2	0.039	17.55	2.540	65.12
	2000	1.5	36	25.6	6.4	0.039	17.99	2.532	64.91
	2000	1.5	30	30.4	10.5	0.035	19.55	2.451	70.04
	**	1.5	36	41.3	22.1	0.017	40.76	1.241	72.99
	2000	1.5	24	38.7	17.2	0.034	20.38	2.274	66.88
x						**0.037**	**18.86**	**2.449**	**66.74**
16	2000	1.5	24	38.1	9.5	0.058	11.95	2.710	46.72
	2000	1.5	24	32.7	13.5	0.037	18.73	2.589	69.98
	2000	1.5	24	33.8	11.3	0.046	15.07	2.747	59.72
						0.047	14.74	2.682	58.81
		*							
x		1..0	24	31.2	18.0	**0.027**	**25.66**	**1.875**	**69.44**

x = individual patient's best estimate of the mean parameter value
* An interruption to CVVHDF therapy occurred during this dosage interval
** CVVHDF was stopped for the duration of this dosage interval.

4.2.3 Pharmacokinetic discussion

This retrospective study demonstrates that vancomycin pharmacokinetic parameters are altered by treatment with CVVHDF. The elimination rate constant is increased by 8-10 fold by treatment with CVVHDF compared to values for undialysed patients with severe renal dysfunction or patients treated with conventional IHD or PD. With CVVHDF, the rate constant is approximately half that reported for patients with normal renal function. Among these sixteen patients treated with CVVHDF, the mean half-life was 16.8 +/- 2.8 hours. This is approximately twice the half-life in patients with normal renal function, but is reduced compared to that observed in non-dialysed anuric patients. The elimination half-life of vancomycin in patients with ESRF ranges from 140-180 hours. Santre et al (149) observed a half-life of 13.9 hours in three patients with oligo-uric acute renal failure undergoing CVVHDF, although lower ultrafiltration rates were used. The ultrafiltration rate was 500ml/hr, compared to a modal rate of 2000ml/hr used in this study. Boereboom (146) reported terminal half-life times of 15.4 and 20.3 hours for two critically ill patients receiving CVVHF and the ultrafiltration rate (1600ml/hr) was closer to the rate used in this study.

Despite large variability in serum concentrations (C_{pmax} range: 18.9 – 41.3 mg/L and C_{pmin} range: 3.7 -22.1 mg/L) and differences in patients' clinical status, there was no great variability in serum half-lives, which were reasonably constant at approximately 17 hours. The percentage coefficient of variation was low, with a value of 16.9%. The mean estimate of the elimination rate constant was 0.043 hr^{-1}.

In critically ill patients, a drug's Vd may vary from that seen in healthy subjects or patients without critical illness or ARF. The mean Vd for

Vancomycin for this sample was 57.48 +/- 12.80 L. The coefficient of variation was 22.3%, reflecting a higher degree of interpatient variability in estimates of Vd, compared with the elimination half-life. The observed Vd was higher than in patients with normal renal function and was higher among patients with oedema than without oedema ($p<0.05$).

Total Body Clearance was estimated (mean +/- sd) as 2.45 +/- 0.62 L/hr. Based on a mean creatinine clearance of 0.3 L/hr prior to commencing CVVHDF therapy and using creatinine clearance as an approximation of vancomycin clearance, CVVHDF results in an 8-fold increase in the TBC of vancomyin. This TBC value was 1.3 – 6.5 times that reported during other forms of CRRT and agrees well with TBC values for vancomycin reported by Santre et al (145) for three patients treated with CVVHDF, who reported a mean value of 2.33 L/hr. A recent prospective study by Deldot et al (147) reported a similar TBC of 2.5 L/hr.

The half-life of vancomycin in patients receiving CVVHDF therapy is less than that reported in patients with severe renal impairment, who are not on Continuous Renal Replacement Therapy, where a prolonged half-life of up to 7 days has been reported.

Vancomycin clearance is generally considered to be approximated by creatinine clearance. Based on the estimated CrCl in this patient sample prior to starting CVVHDF (0.3L/hr) and a Vd of 60L, a rough estimate of k prior to CVVHDF would be of the order of 0.005 hr^{-1}. This represents a half-life of 138.6 hours, which is far longer than the mean of 16.8 hours observed during CVVHDF, and indicates a greater than 8-fold increase in the elimination rate constant during CVVHDF. Vd values are slightly higher than normal but exhibit intra- and inter-patient variability. The combination of convective and

diffusive clearances together with the high ultrafiltration rates in use resulted in higher vancomycin clearance than observed in earlier studies, where less efficient forms of CRRT and lower ultrafiltration rates were employed. Results are compared with published values in Table 4.2.3.

Table 4.2.3: Comparison of estimated vancomycin pharmacokinetic parameters during CVVHDF with published values.

Author/Year of Publication	Type of CRRT	Half-life (hours)	TBC (L/hr)	Vd (L)	Dosage recommendations
Current study N=16	CVVHDF	16.8 +/- 2.8	2.45 +/- 0.62	57.48 +/- 12.80	1.0g – 1.5g once daily, depending on Vd, levels and effluent rates.
Deldot (2004) N=10	CVVHDF	16.6 +/- 8.7	2.5 +/- 0.7	49.7 +/- 29.1	750mg/12 hours
Santre (1993) N=3	CVVHDF	13.9	2.3 +/- 0.3	47.4 +/- 6.41	7.5mg/kg/12hrs
Boereboom (1999) N=2	CVVH	17.9	1.95	48.76	15-20mg/kg initially, after 24 hours; 250-500mg/12 hours
Joy (1998) N=4	CVVHF (Stable patients)		1.37 (Haemo filter clearance)		850-1050mg/24 hours
Macias (1991) N=10	CVVHF		1.7 +/- 0.4		750-1500mg/24 hours
Bellomo (1998)	CAVHD		0.64		500mg or more/24 hours
Davies (1992) N=10	CAVHD/CVVHD	24.7 +/- 2.6	1.86 +/- 0.28	60.7 +/- 5.11	1000mg/48 hours
Dupuis (1989) N=1	CAVH	45	0.38		
Matzke (1986) N=5	Intermittent Haemofiltration (ESRF patients)	4.1 +/- 1.2	9.2 +/- 1.3		18mg/kg immediately after haemofiltration

4.2.4 Clinical Discussion

In terms of assessing the likelihood of clinical efficacy of Vancomycin therapy, the most appropriate PK-PD goal is maintaining vancomycin serum concentrations above the MIC of susceptible bacteria. Because the average vancomycin MIC values for S. aureus and S. epidermidis are 1 to 2 mg/L, if we want to maintain serum concentrations four to five times above the MIC, trough levels of at least 5 or 10mg/L with MIC values of 1 or 2mg/L respectively, appear reasonable. This was the rationale behind the target trough concentration range, of 5-12mg/L, in use. However, a more recent study indicates that vancomycin trough concentrations of 10 to 15mg/L and peak concentrations greater than 25mg/L are optimal for MRSA-related pneumonia and bacteremia (152). In addition, therapeutic failures have been reported in patients with endocarditis with trough concentrations, less than 10mg/L (153). The most commonly prescribed dosage regimen during CVVHDF was 1g every 24 hours. The range of trough concentrations achieved by this dosing schedule was 3.7 – 12.4mg/L. Trough concentrations at the lower end of this range, particularly concentrations < 5mg/L, will present an increased risk of therapy failure. Higher doses (>1g) or preferably a shorter dosage interval (closer to the estimated half-life), may be necessary in some patients, with an increased Vd or Clearance, or when treating more resistant strains, in order to ensure adequate trough concentrations for bacterial killing.

The range of peak concentration achieved with this dosing schedule was 20.8mg/L – 34.9 mg/L. The range of peak serum sampling times was 60 – 80 minutes after the infusion was complete (mean = 64 minutes). The duration of the infusion ranged from 100 minutes to 120 minutes (mean 116 minutes). All peak concentrations were within the target range of 20-40mg/L.

The mean C_{pmin} or 'trough' concentration estimated in this study was 11.3 +/- 3.6mg/L, which is at the higher end of the stated target range (5-12mg/L). This observation may reflect current opinion that higher trough concentrations may be required in some patient populations, such as the critically ill, particularly for MRSA infection or endocarditis. Ideally, individualized target serum concentrations should be selected for each patient. Low and borderline target concentrations in these patients are of concern, due to the associated risks of therapy failure and the development of resistance.

4.3 A Prospective Pharmacokinetic Evaluation of Vancomycin in Critically Ill Patients treated with CVVHDF

4.3.1 Patients

Thirteen patients were enrolled in the study. The mean age was 60.8 +/- 15.0 years. Patient demographic and clinical information are presented in Table 2.3.1. There were no adverse effects attributable to the use of vancomycin in this study population. Of the thirteen patients treated, only one patient was treated empirically. The remaining patients were all treated with Vancomycin for documented gram-positive infections. Six patients were MRSA positive and Vancomycin-Resistant Enterococcus species were isolated during the treatment of one patient. Nine patients were diagnosed with sepsis. Sepsis (and its treatment) increases renal preload and via capillary permeability, leads to an increased Vd, which can increase antibacterial clearance. However, sepsis can induce multiple organ dysfunction, including ARF (but also hepatic dysfunction), resulting in a decrease in antibacterial clearance. Five patients had serious concurrent hepatic impairment. The mean APACHE Π score was 25.46 +/- 4.03 and the mean SOFA score was 8.15 +/- 2.37. The mean duration of CVVHDF therapy was 11.5 +/- 5.9 days. The mean ultrafiltration rate during CVVHDF was 2.02L/hr and the mean dialysis fluid rate was 1.11L/hr. The actual flow rates achieved were measured by collection of effluent fluid. The mean effluent fluid flow rate was 3.13 +/- 0.44 L/hr. The mean duration of use of a filter was 48.7 hours. In the case of Patients 2 (Profile B), 7 (PB), 10 (PC), 11 (PB) and 13 (PB), the full serum profile was obtained while changing to a second filter circuit, when CVVHDF was interrupted due to clotted filters requiring change. For Patients 11 (Profile D) and 12 (PD), filter changes occurred when the duration of use of the filter had exceeded the recommended

duration of 72 hours, at 76 hours for 11D and 79 hours for 12D. The time off filter was 0.32 hr (1.3%) and 0.42 hr (1.8% of dosage interval) respectively. All patients had severe renal impairment (CrCl < 10ml/min). The method of Jelliffe and Jelliffe was used to estimate CrCl, in an attempt to avoid error due to patient's deteriorating renal function. However, as seven patients were anuric, while the remaining six patients were oliguric, it is unlikely to be an accurate assessment of residual renal function. Creatinine clearance by the filter was directly measured and is discussed later in this chapter. Only two patients had severe renal impairment prior to this Hospital admission. Both of these patients had chronic renal failure. The patient with ESRF had been previously dialyzed, but on admission was haemodynamically unstable and treatment with IHD was considered unsuitable.

Table 4.3.1: Patient Demographics and Clinical Characteristics

ID	Sex	Age	Diagnosis	Infective Diagnosis	APACHE II score	SOFA score	Sr Cr[1]	Cr Cl[2]	Duration CVVHDF
1	M	57	MSOF, septic shock, anuric	Coagulase negative staphlococci (blood)	28	11	239	4	25
2	F	63	Post hemicolectomy, Sepsis, ARF, Oliguric	Coagulase negative staphylococci (blood), MRSA E. faecium (wound), VRE, candida albicans	24	7	131	6	11
3	M	62	Emergency admission to ICU post leaking AAA repair, Cirrhosis of liver, oliguric	Candida albicans, coagulase negative staphylococci (blood)	30	11	119	7	15
4	M	30	Multiple trauma Sepsis, oliguric	Coagulase negative staphylococci, Pseudomonas, Klebsiella pneumoniae (blood)	21	7	152	9	6
5	F	71	Acute on chronic renal impairment, ESRD, Sepsis, anuric	Empiric cover	19	6	407	3	8
6	M	77	Post right hemicolectomy, Metabolic acidosis, Chronic renal impairment, Type 2 DM, Atrial fibrillation Anuric	Coagulase negative staphylococci (blood), Klebsiella pneumoniae (bronchial), MRSA	26	5	391[3]	2	19
7	M	48	Recurrent acute pancreatitis 2y increased lipids/cholesterol, extensive varicosities, endocrine insufficiency, respiratory failure, Sepsis,anuric, pyrexia	Coagulase negative Staphylococci (blood) MRSA	28	10	307	4	11
8	F	79	ARF, Sepsis, CAP, IHD, HTN, COPD, anuric	Coagulase negative staphylococci	28	10	136	5	4
9	M	57	Cirrhosis of liver, Acute renal failure, sepsis, anuric thrombocytopenia, metabolic acidosis, hypoalbuminaemia	Actinetobacter baumanni, E. Faecalis, P. aeruginosa, Coag. negative staphlococci	29	11	120	9	7
10	M	62	Postop Aortobifemoral bypass,	Gram positive coccus in BC	23	7	118	8	6

			hypotension, ARF, oliguric						
11	F	68	Emergency Hartman's procedure for Colonic obstruction, post-op acute renal failure and sepsis, anuric, coagulopathy	Enterococcus faecalis, Pseudomonas aeruginosa, MRSA	31	9	130	7	14
12	M	78	Sepsis, Atrial fibrillation, liver impairment, oliguric	S. aureus, MRSA. E.coli, Citrobacter freundii, Klebsiella pneumoniae, Clistridium perfringens	19	4	107	8	14
13	M	38	Sepsis, pyrexia, respiratory failure	MRSA, candida (non-albicans)	25	8	112	9	9

[1] on day one of CVVHDF therapy; units = μmol/L; level taken prior to commencing CVVHDF therapy.
[2] estimated using the Jelliffe and Jelliffe method on day 1 CVVHDF therapy; units ml/min
[3] value on starting CVVHDF, 208μmol/L on starting vancomycin

4.3.2 Pharmacokinetic Analysis of Vancomycin Serum Concentration Data

Thirty-eight pharmacokinetic data sets were obtained from these thirteen patients. Pre-dose (trough) and 'peak' concentrations were obtained for all dosage intervals. Additionally, multiple serum samples in a dosage interval were obtained for at least one dosage interval for each patient, in order to compare estimates of vancomycin pharmacokinetic parameters during CVVHDF therapy, obtained using two serum concentrations (peak and trough) versus those derived from multiple serum concentrations in a dosage interval. One objective of the prospective study was to assess the validity of using TDM data (2 serum concentrations in a dosage interval), which requires the use of a one-compartment model, to estimate individual patients' pharmacokinetic parameters for vancomycin during CVVHDF therapy. In order to do this, multiple vancomycin serum concentrations in a single dosage interval were monitored, which allowed the use of a 2-compartment model to calculate

pharmacokinetic parameters. Initially, the vancomycin concentration-time data was fitted to a 2-compartment model and pharmacokinetic parameters (k_{β}, kel, $t_{1/2\beta}$, V_1, Vd_{ext}, TBC etc) were estimated. The same multiple serum concentrations – time data was then fitted to a one compartment model and estimates of k, Vd ($t_{1/2}$, TBC) were calculated and compared with estimates of k_{β}, Vd_{ext} ($t_{1/2\beta}$,Cl) derived using a 2-compartment model. These one-compartment model parameter estimates (k, V, $t_{1/2}$, Cl) determined using multiple serum concentrations were then compared with those calculated from two serum concentrations only (TDM type data: 'peak' and trough concentrations) on the basis of a one-compartment model (Sawchuk/Zaske approach).

Linear and semi-log plots of the vancomycin serum concentration-time data, obtained from multiple serum concentrations in a dosage interval, are presented in Fig 4.3.1.

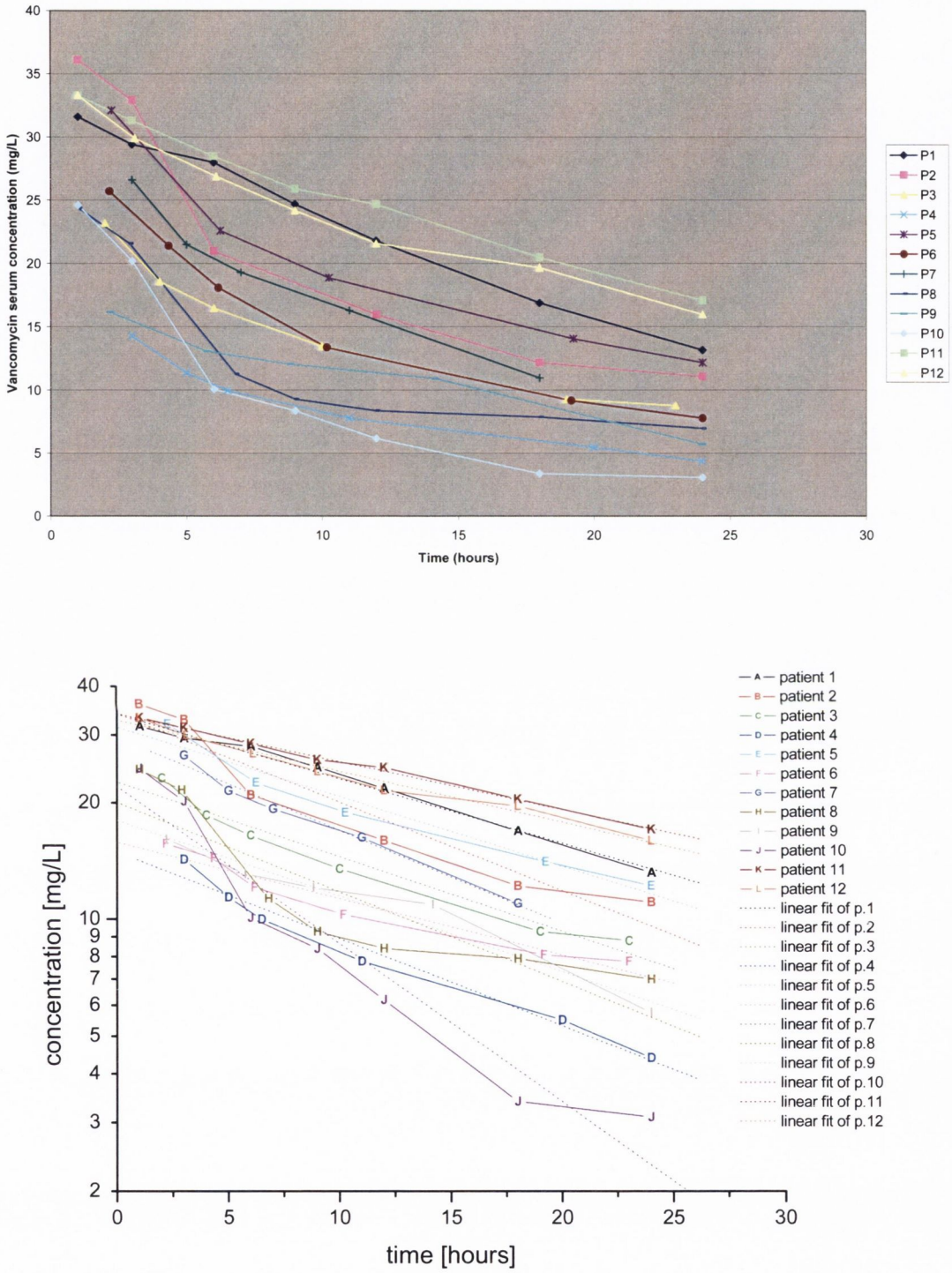


Figure 4.3.1: Linear and semilog plots of Vancomycin serum conconcentration-time data (multiple serum samples in a dosage interval)

4.3.3 Comparison of the use of a two-compartment model versus a one-compartment model for determining individual patient estimates of vancomycin pharmacokinetic parameters during critical illness and treatment with CVVHDF.

The best-fit parameters of both mono- and bi- exponential models for each patient are included with individual estimates of PK parameters in Tables 4.3.2 and 4.3.3.

Published data has used both one and two exponential models to examine vancomycin pharmacokinetics, as discussed in section 4.1.3. The fit was slightly better with a two-compartment model, as indicated by a higher MSC, r^2 and correlation when the data was fitted according to a biexponential equation.

4.3.4 Estimation of Pharmacokinetic Parameters

Using the approach suggested by Wagner, described in section 2.8 (Introduction), calculations from the fitting of the post-infusion data were used to write the corresponding equation for bolus intravenous injection. The fitted post-infusion data gave the value of λi and the infusion time, T, was known. Thus, the coefficient corresponding to bolus intravenous injection was calculated using equation 1.2.8.2. The equations for bolus intravenous injection, described in section 1.2.7, were then applied to obtain k_{β}, Vd_{ext}, TBC etc.

The parameters, A, B, α and β were determined using Micromath Scientist 3.0, by fitting the vancomycin serum concentration data to a biexponential model. These parameters were used to estimate k_{el}, k_{β}, V_1, V_{dext} and V_{darea}.

Individual patient estimates of k_{el} were obtained from α and β using equation 1.2.7.7. The mean (+/- sd) value of k_{el} was 0.051 +/- 0.014 hr^{-1}. Estimates of $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2el}$ were determined for each patient from α, β and k_{el} using

equations 1.2.7.10, 1.2.7.9, 1.2.2.7. Individual patient estimates of each parameter are included in Table 2.3.2. The values of β and k_{el} were similar, resulting in close agreement between estimates of $t_{1/2\beta,}$ and $t_{1/2el}$. Thus, β may be considered to be the apparent rate constant for elimination. The magnitude of β was compared with k, the elimination rate constant for a one-compartment model. The estimated $t_{1/2\beta}$ was compared with the one-compartment model elimination half-life, t1/2.

V_1 was estimated from equation 2.7.5. The mean value was 52.86 +/- 8.54 L. V_1 is the volume of the central compartment and will be compared with the estimate of Vd for the one-compartment model. V_{darea} was estimated from equation 2.7.11. The mean +/- sd value of V_{darea} was 55.91 +/- 16.33 L. V_{dext} was calculated from equation 2.7.13. The mean estimate of V_{dext} was 63.31 +/- 14.08 L. The mean (+/- sd) TBC value was 2.883 +/- 1.126 L/hr, as determined using equation 1.2.7.15. Estimates of individual patient parameters are given below in Table 4.3.2:

Table 4.3.2: Estimates of individual patient vancomycin pharmacokinetic parameters derived from multiple serum concentrations in a single dosage interval (2-compartment model)

ID	k_{el} (hr^{-1})	V_1 (L)	V_{dext} (L)	TBC (L/hr)	$t_{1/2\alpha}$ (hrs)	$t_{1/2\beta}$ (hrs)	$t_{1/2el}$ (hrs)	Least sum of squares	MSC	R^2	Corr.
1	0.044	64.36	71.23	2.831	0.86	16.21	15.75	0.00559	2.89	0.9912	0.9715
2	0.054	42.31	46.92	2.285	0.79	12.92	12.83	0.00589	2.74	0.9905	0.9608
3	0.051	53.86	61.27	2.747	0.45	14.01	13.59	0.00549	2.85	0.9936	0.9755
4	0.058	65.78	81.47	3.815	0.36	12.36	11.99	0.00496	3.18	0.9945	0.9810
5	0.048	37.25	40.09	1.788	0.91	14.98	14.44	0.00512	3.07	0.9916	0.9812
6	0.030	50.11	82.75	1.503	0.51	21.75	23.10	0.00489	3.46	0.9965	0.9687
7	0.048	48.02	60.12	2.305	0.71	14.75	14.45	0.00501	3.01	0.9929	0.9785
8	0.061	50.62	51.47	3.088	0.77	11.41	11.37	0.00487	3.20	0.9932	0.9797
9	0.062	51.11	57.86	3.169	0.39	11.10	11.19	0.00522	3.31	0.9902	0.9801
10	0.080	61.11	62.01	4.888	0.81	8.91	8.96	0.00397	3.98	0.9964	0.9881
11	0.033	48.9	70.48	1.614	0.69	23.27	21.05	0.00410	3.51	0.9957	0.9801
12	0.036	51.2	52.74	1.843	0.92	19.86	19.25	0.00610	2.70	0.9872	0.9704
13	0.057	62.57	84.57	4.820	0.17	12.83	12.15	0.00501	3.37	0.9902	0.9898

Albrecht et al (154) established that the vancomycin distribution half-life was in the range 0.16-0.76 hour and their data indicate that a one-compartment model using two serum concentrations is acceptable for pharmacokinetic studies. The vancomycin distribution half-life for our sample was slightly more variable with a range of 0.17-0.92 hour (mean 0.61 +/- 0.25). On average, the distribution phase was complete 2.01 hours after the start of the infusion.

The one-compartment model equations for multiple dose constant rate infusions, used to obtain estimates of k, Vd, $t_{1/2}$ and Cl are discussed in section 2.5 (Introduction). These equations were applied to the vancomycin serum

concentration-time data fitted to a one-compartment model. Estimates of individual patient parameters (mean (+/- sd) values) obtained by applying a one-compartment model to vancomycin serum concentration-time data, for a single dosage interval during CVVHDF therapy, are given in Table 4.3.3:

Table 4.3.3: Estimates of individual patient vancomycin pharmacokinetic parameters derived from multiple serum concentrations in a dosage interval using a one-compartment model.

Patient ID	k (hr^{-1})	Vd (L)	TBC_{mono} (L/hr)	Least sum of squares	MSC	R^2	Corr.
1	0.041	70.601	3.111	0.00668	2.73	0.9896	0.9698
2	0.051	45.892	2.478	0.01030	2.71	0.9878	0.9512
3	0.049	55.556	2.833	0.00599	2.79	0.9926	0.9745
4	0.055	71.429	4.143	0.00696	2.74	0.9899	0.9610
5	0.047	38.714	1.858	0.00611	2.78	0.9906	0.9712
6	0.029	50.127	1.504	0.00701	2.73	0.9876	0.9687
7	0.048	48.451	2.326	0.00515	2.98	0.9939	0.9730
8	0.060	49.619	3.027	0.00497	3.14	0.9946	0.9789
9	0.061	58.823	3.647	0.00508	3.01	0.9942	0.9793
10	0.079	55.336	4.427	0.00482	3.46	0.9954	0.9781
11	0.033	52.510	1.732	0.00410	3.51	0.9957	0.9801
12	0.035	53.571	1.929	0.00610	2.70	0.9872	0.9704
13	0.057	66.677	3.802	0.00518	3.07	0.9912	0.9798

Paired student t-tests were carried out on estimates of pharmacokinetic parameters obtained using both models. The parameters compared were k (1-compartment elimination rate constant) and k_{el}, Vd and V_1, and TBC_{mono} (k. Vd) and TBC_{biexp} ($V_1.k_{el}$). The estimates of pharmacokinetic parameters determined using a 2-compartment model, with multiple serum concentrations did not differ significantly from those obtained by applying a one-compartment model to the same serum concentration data ($p>0.05$), as shown in Table 4.5.6. These estimates were calculated first for individual patients and the mean +/- sd values were then determined. The elimination parameters derived from a one and two compartment model were compared. For a one-compartment model, first order elimination

assumes immediate and uniform, complete distribution into a single compartment followed by elimination; k is the elimination rate constant and is equal to the slope of the line of the log concentration versus time plot. With a two-compartment model, distribution is considered to occur initially into a central compartment followed by a gradual equilibration with a peripheral compartment; k_{β} is the hybrid elimination rate constant for a two compartment model. If a two-compartment model collapses to a one-compartment model, the values of k_{el} and k should be similar. In order to assess whether a one-compartment model is adequate to obtain estimates of k for individual patients, the calculated value of k_{el} (from a two-compartment model) was compared to the estimated k (1-compartment model elimination rate constant). Cl_{mono} is the estimated TBC obtained using a one-compartment model, from the product of k and Vd. Cl_{biexp} is the estimated TBC derived from a two-compartment model from the product of k_{el} and V_1.

Table 4.3.4a: Comparsion of individual patient estimates of vancomycin pharmacokinetic parameters obtained using a one- versus a two-compartment model.

Patient[1]	k (hr^{-1})	k_{el} (hr^{-1})	Vd (L)	V_1 (L)	$TBC_{monoexp}$ (L/hr)	TBC_{biexp} (L/hr)
1	0.041	0.044	70.60	64.36	3.111	2.831
2	0.051	0.054	45.89	42.31	2.478	2.285
3	0.049	0.051	55.56	53.86	2.833	2.747
4	0.055	0.058	71.43	65.78	4.143	3.815
5	0.047	0.048	38.71	37.25	1.858	1.788
6	0.029	0.030	50.13	50.11	1.504	1.503
7	0.048	0.048	48.45	48.02	2.326	2.305
8	0.060	0.061	49.62	50.62	3.027	3.088
9	0.061	0.062	58.82	51.11	3.647	3.169
10	0.079	0.080	55.34	61.11	4.427	4.888
11	0.033	0.033	59.90	48.9	1.732	1.614
12	0.035	0.036	53.57	51.2	1.929	1.843
13	0.057	0.057	66.68	62.57	3.802	4.820

Table 4.3.4b: Comparison of sample mean estimates of vancomycin parameters during CVVHDF therapy derived using one-and two-compartment models

Parameter	**k**	**k_{el}**	**p>0.05**
Mean (sd)	0.050 +/- 0.013	0.051 +/- 0.014	NSS
Parameter	**Vd**	**V_1**	
Mean(sd)	55.177 +/- 9.645	52.862 +/-8.539	NSS
Parameter	**TBC_{mono}**	**TBC_{biexp}**	
Mean(sd)	2.832 +/- 0.962	2.883 +/- 1.126	NSS

Although a 2-compartment model gave a better fit than a one-compartment model, a confidence interval comparison of estimated pharmacokinetic parameters showed no significant differences between the one and two compartment models. The value of k_{el} was closely approximated by the value of k; the value of V_1 was slightly less than the value of Vd and estimates of TBC were similar using both models. The comparable estimates of individual patient pharmacokinetic parameters obtained using both models validates the use of a one-compartment model for the purpose of estimating vancomycin pharmacokinetic parameters for individual patients during treatment with CVVHDF. According to Wagner (155), when elimination is only from the central compartment, the two compartment open model essentially collapses to the one compartment open model. The two compartment open model collapses to the one compartment model as $(B/A+B) \rightarrow 1$ or as $V_1 \rightarrow V_{dext.}$ The ratio of (B/A+B) was estimated as 0.84 and the values of V_1 and V_{dext} were reasonable close. The respective 95% CIs for $V_{1\ and}$ V_{dext} were 36.12 – 69.598 and 35.46 - 90.90 L. The inverse ratio, β/k_{el} indicates how 'two-compartment' a particular drug is and the smaller the ratio the greater the amount of drug in the second compartment, compared with the first. The ratio of β/k_{el} among this sample was large (0.91). This may explain why the one-compartment model can be used to simplify dosage regimen calculations and why the one-compartment open model gives adequate predictions of average amounts of drug in the body at equilibrium state despite the fact that the data really obey the two compartment open model (155).

4.3.5 Estimation of Vancomycin Volume of Distribution using non-compartmental methods

In the previous sections, determination of the volume of distribution (Vd, Vd_{ext}) has been model-dependent. Vd was calculated on the basis of a one-compartment model and Vd_{ext} was determined using a 2-compartment model. An alternative approach is to use non-compartmental methods to estimate Vd_{ss}. Estimates of Vd_{ss} were obtained for each patient from the multiple serum vancomycin concentrations in a dosage interval. AUCs were calculated using the linear trapezoidal rule. The volume of distribution at steady state (Vd_{ss}) was calculated as dose x (AUC_{0-24} + 24 X C_{24}/λ_Z)/$(AUC_{0-24})^2$. These values were compared with previously calculated values for Vd and Vd_{ext}, using multiple serum concentrations in a dosage interval. Calculated values of Vd_{ss} for individual patients are given in Table 4.3.5. Mean Vd_{ss} estimates slightly exceeded Vd estimates but were less than Vd_{ext} values. Vd_{ext} was not significantly different to Vd_{ss}. The 95% C.I.s for Vd_{ext} and Vd_{ss} were 35.144 – 90.905 and 37.196 – 85.314 L respectively.

Table 4.3.5: Comparison of estimates of V_1, Vd_{ext} and Vd obtained using compartmental models with Vd_{ss} obtained using a non-compartmental approach.

Patient ID	Vd_{ss} (L)	V_1 (L)	V_{dext} (L)	Vd (L)
1	71.091	64.36	71.23	70.601
2	45.812	42.31	46.92	45.892
3	59.998	53.86	61.27	55.556
4	77.103	65.78	81.47	71.429
5	40.101	37.25	40.09	38.714
6	76.420	50.11	82.75	50.127
7	58.782	48.02	60.12	48.451
8	51.001	50.62	51.47	49.619
9	56.032	51.11	57.86	58.823
10	60.755	61.11	62.01	55.336
11	67.821	48.9	70.48	52.510
12	53.021	51.2	52.74	53.571
13	78.373	62.57	84.57	66.677

Non-compartmental methods can be used to obtain estimates of vancomycin pharmacokinetic parameters from multiple serum concentrations in a dosage interval-time, which are comparable with those calculated, using a 2-compartment model from the same multiple serum concentration-time data.

4.3.6 Pharmacokinetic analysis of 'peak' and trough vancomycin serum concentrations

Estimates of pharmacokinetic parameters obtained from 'peak' and trough concentrations, calculated using the method of Sawchuk and Zaske, on the basis of a one-compartment model are presented in Table 4.3.6. These individual patient pharmacokinetic parameters were obtained using routine TDM data i.e. 'peak' (extrapolated to C_{pmax}) and trough concentrations only. This was the approach used to analyze the retrospective data. However, this prospective data was collected on designated data collection forms, following staff induction and as such was 'simulated TDM' data. Estimates of k, Vd, $t_{1/2}$ and Cl were calculated using this approach and compared with those obtained by fitting multiple serum concentrations in a dosage interval to a one-compartment model (Table 4.3.8). Estimates of k, Vd, $t_{1/2}$ derived from two serum concentrations (TDM 'peak' and trough concentrations) did not differ significantly from parameter values obtained from multiple serum concentrations in a dosage interval, analysed using a one compartment model.

Table 4.3.6: Pharmacokinetic parameters estimated from C_{pmax} and C_{pmin} vancomycin concentrations using the 'Sawchuk and Zaske' method.

ID	UF rate (L/hr)	Dose (g)	τ (hrs)	C_{pmax} (mg/L)	C_{pmin} (mg/L)	$t_{1/2}$ (hrs)	k (hr^{-1})	Cl (L/hr)	Vd (L)
1A	2.0	1.5	24	31.6	13.2	**16.67**	**0.042**	**3.033**	**72.22**
2A	2.0	1	16	37.6	13.1	8.54	0.081	2.826	34.89
2B	2.0	1	18	30.8	15.3	14.86	0.047	2.644	56.26
2C	2.0	1	29	36.1	11.1	14.69	0.047	1.821	38.75
2D	2.0	1	24	28.1	9.6	13.55	0.051	2.495	48.93
Mean						**12.91**	**0.057**	**2.447**	**44.71**
3A	2.0	1	24	23.2	8.8	15.07	0.046	2.900	63.04
3B	2.1	1	24	22.3	7.9	14.14	0.049	3.072	62.69
3C	2.0	1	24	22.1	7.6	13.59	0.051	3.182	62.39
Mean						**14.27**	**0.049**	**3.051**	**62.71**
4A	2.1	1	24	14.3	4.4	12.34	0.056	5.110	91.26
4B	2.1	1	18	16.7	6.4	13.00	0.053	4.354	82.15
Mean						**12.67**	**0.055**	**4.732**	**86.71**
5A	2.0	1	24	32.1	12.2	15.07	0.046	2.095	45.55
5B	1.8	1	24	35.6	13.6	15.07	0.046	1.895	41.19
5C	1.7	1	24	36.5	13.8	15.07	0.046	1.838	39.95
Mean						**15.07**	**0.046**	**1.943**	**42.23**
6A	2.0	1	23	25.7	7.8	11.55	0.060	3.010	50.17
6B	2.0	1	24	23.5	13*	24.75	0.028	2.430	86.77
6C	2.1	1	24	25.8	15*	27.72	0.025	2.115	84.59
Mean						**21.34**	**0.038**	**2.518**	**73.84**
7A	2.0	1	18	26.6	11.0	14.14	0.049	2.807	57.29
7B	2.1	1	18	26.3	11.2	14.74	0.047	2.785	59.26
7C	2.0	1	18	30.9	14.6	16.50	0.042	2.305	54.88
Mean						**15.13**	**0.046**	**2.632**	**57.14**
8A	2.0	1	24	24.4	7.0	11.69	0.059	3.061	51.88
8B	2.0	1	24	24.8	7.1	11.55	0.060	3.056	50.94
8C	2.0	1	24	25.7	7.4	11.69	0.059	2.899	49.14
Mean						**11.64**	**0.059**	**3.005**	**50.65**
9A	2.0	1	24	16.2	5.7	10.97	0.050	4.309	86.18
9B	2.0	1	24	21.1	5.6	11.0	0.063	3.650	57.94
Mean						**10.99**	**0.057**	**3.980**	**72.06**
10A	2.0	1	12	16.8	8.1	9.50	0.072	4.045	75.01
10B	2.0	1	12	21.2	7.2	6.48	0.107	5.702	57.33
10C	2.0	1	12	22.6	14.11	13.2	0.052	3.958	76.12
Mean						**9.73**	**0.075**	**4.568**	**69.48**
11A	2.1	1	24	25.2	12.8	21.48	0.032	2.349	73.42
11B	2.2	1	24	28.5	15.2	23.15	0.030	2.053	68.42
11C	2.0	1	24	31.5	17.9	25.75	0.027	1.809	67.02
11D	2.0	1	24	33.3	17.1	21.84	0.031	1.690	56.33
Mean						**23.06**	**0.030**	**1.975**	**66.30**
12A	2.2	1	24	17.5	4.9	11.43	0.061	4.363	71.52
12B	2.0	1	24	29.5	12	16.18	0.043	2.233	51.94
12C	2.0	1	24	33.3	16	19.85	0.035	2.839	52.54
12D	1.0	1	24	37.0	15	16.17	0.043	1.773	41.23
12E	1.0	1	24	34.3	15	17.59	0.039	1.778	45.59
Mean						**16.24**	**0.044**	**2.595**	**52.57**
13A	2.1	1	24	18.9	3.6	8.77	0.079	4.618	58.45
13B	2.0	1	24	17.1	3.1	8.56	0.081	5.170	63.83
13C	2.0	1	24	24.6	3.1	7.03	0.099	4.071	41.12
13D	2.0	1.5	18	33.9	8.2	8.79	0.078	4.971	63.74
13E	2.0	1.5	18	34.2	10.4	10.47	0.066	4.485	67.95
Mean						**8.72**	**0.081**	**4.663**	**59.02**

* Interruption to CVVHDF during this dosage interval

For the same vancomycin serum concentration data set in the same patients, the 95% C.I. for k estimated using the SZM (2 serum concentrations) (0.019 hr^{-1} – 0.089 hr^{-1}) was wider than but included the 95% C.I. for k calculated using multiple serum concentrations in a dosage interval and a one-compartment model (0.025 hr^{-1} -0.075 hr^{-1}). Similarly, the 95% C.I. for Vd as estimated using the SZM was slightly more variable than the 95% C.I. for Vd calculated using multiple serum concentrations (95% C.I.: 36.821 – 88.761 (SZM) vs. 36.273 – 74.081 (multiple sampling). The 95% C.I. for TBC estimated using the SZM was narrower and coincided with the 95% C.I. for TBC estimated using multiple serum concentrations.

Table 4.3.7a: Comparison of 1-compartment model estimates of Vd, k and TBC, estimated using two serum concentrations versus multiple serum concentrations in the same dosage interval.

Patient ID	k_{SZM} (hr^{-1})	k (hr^{-1})	Vd_{SZM} (L)	Vd (L)	TBC_{SZM} (L/hr)	TBC (L/hr)
1	0.042	0.041	72.22	70.601	3.033	3.111
2	0.057	0.051	44.71	45.892	2.447	2.478
3	0.049	0.049	62.71	55.556	3.051	2.833
4	0.055	0.055	86.71	71.429	4.732	4.143
5	0.046	0.047	42.23	38.714	1.943	1.858
6	0.038	0.029	73.84	50.127	2.518	1.504
7	0.046	0.048	57.14	48.451	2.632	2.326
8	0.059	0.060	50.65	49.619	3.005	3.027
9	0.057	0.061	72.06	58.823	3.980	3.647
10	0.081	0.079	59.02	55.336	4.663	4.427
11	0.030	0.033	66.30	52.510	1.975	1.732
12	0.044	0.035	52.57	53.571	2.397	1.929
13	0.095	0.057	76.13	66.677	4.764	3.802

Table 4.3.7b: Comparison of confidence intervals for k, Vd and TBC for vancomycin during CVVHDF therapy estimated using two serum samples in a dosage interval versus multiple serum samples in a dosage interval (one-compartment model).

Parameter	95% C.I. calculated using two serum concentrations in a dosage interval	95% C.I. calculated using multiple serum concentrations in a dosage interval
k (hr^{-1})	0.019 – 0.089	0.025 - 0.075
Vd (L)	36.821 – 88.76	36.273 – 74.081
TBC (L/hr)	1.228 – 5.101	0.946 - 4.718

4.3.7 Clinical Observations and Pharmacokinetic Discussion

Elimination half-life is the descriptor used most often by pharmacists and clinicians to describe a drug's pharmacokinetic behaviour. The mean elimination half-life value for this patient sample was 14.39 +/- 4.34 hours and this corresponds to a mean elimination rate constant of 0.054 +/- 0.018 hr^{-1}. The elimination half-life is prolonged compared to normal renal function but is lower than in non-dialysed patients with severe renal impairment. It ranged from 8.7 hours (patient 13 best estimate) to 23 hours (patient 11 best estimate of $t_{1/2}$).

Patient 13 was a 38 year old male with sepsis, severe burns and respiratory failure. He was admitted to ICU following a RTA. He had no pre-existing renal impairment or co morbidities. He developed ARF, with persistent oedema and CVVHDF therapy was initiated due to fluid overload. A very high mean Vd (76L) was noted, which contributed to the high TBC. Increased Vancomycin clearance in critically ill patients and patients with extensive burns has been previously reported (110).

Patient 11 developed ARF and sepsis post-operatively following an emergency

Hartman's procedure for colonic obstruction. This patient was anuric throughout treatment and CVVHDF was run heparin-free, due to coagulopathy. However, there were only two filter clots during CVVHDF therapy and filter replacement occurred within 30 minutes in both cases (18 minutes, 26 minutes). A serum sample was taken as soon as CVVHDF was stopped and restarted, in order to obtain a complete Vancomycin profile during CVVHDF therapy. Analysis of the vancomycin effluent concentration data for this patient revealed that almost all of the vancomycin eliminated in a dosage interval was removed by CVVHDF.

The mean estimate of the elimination half-life is slightly lower but not significantly different ($p>0.05$) from the mean estimate in the retrospective sample (16.8 +/- 2.8 hours) and the coefficient of variation is higher (30%) (Table 4.2.3). The mean TBC was 3.3 +/- 1.5 L/hr. This represents clearance due to CVVHDF, in addition to clearance due to any residual renal function or non-renal routes. The clearance component due to CVVHDF will be analysed and discussed in the next section of this chapter.

Table 4.3.8: Comparison of confidence intervals for estimates of k, Vd and Cl for vancomycin during CVVHDF therapy, derived from the retrospective and prospective analyses.

Parameter	95% C.I. for vancomycin parameter estimates during CVVHDF derived from retrospective data	95% C.I. for vancomycin parameter estimate during CVVHDF calculated prospectively.
k (hr^{-1})	0.018 – 0.065	0.015 – 0.089
Vd (L)	32.391 – 82.576	31.131 – 73.236
TBC (L/hr)	1.230 – 3.672	1.127 - 4.275

The mean Vd was 62.8 +/- 13.3 L. The coefficient of variation was 21.2%, which was indicative of a similar level of inter-patient variability to that seen in the retrospective study (%CV = 22.3%). The intra-patient coefficient of variation was as high as 28%, as observed in Patient 6. Intra- and inter-patient variability in observed Vd values complicate dosing in these patients. Higher doses will be required to achieve therapeutic serum concentrations when increases in Vd are observed, but changes in Vd during CVVHDF therapy may require further dosage modification. Changes in Vd during critical illness and in particular during CVVHDF are inevitable and must be a consideration, in addition to sieving coefficients and ultrafiltration rates, when optimising dosing schedules.

A dosing schedule of 1g vancomycin every 24 hours remained the mainstay of therapy. This was considered a rationale dosage regimen during CVVHDF therapy, due to the finding in the retrospective study that the elimination half-life was on average double that seen in patients with normal renal function. However, it was emphasised that individualised dosage adjustment was

essential given the level of variability in vancomycin serum concentrations and pharmacokinetic parameters during CVVHDF therapy and the need for an assessment of target serum concentrations.

For nine of the thirteen patients, a dosing schedule of 1g every 24 hours was adopted. In one patient, a higher dose of 1.5g was administered and for three other patients, shorter dosage intervals were used.

The lowest C_{pmin} concentration (3.3mg/L) was observed in Patient 10. The estimated vancomycin TBC for this patient was high, with a mean value of 4.7L/hr. In response to these serum concentrations and estimated pharmacokinetic parameters, the dosing schedule was modified, with an increase in the dose (1.5g) and a shortening of the dosage interval (18 hours). This dosage adjustment achieved target serum concentrations. The mean C_{pmax} and C_{pmin} concentrations for the CVVHDF treatment period were 26.8 +/- 6.4 mg/L and 10.2 +/- 4.2mg/L respectively.

Large variations in vancomycin serum concentrations were observed in patients receiving the same vancomycin dosing schedule and under similar CVVHDF conditions, due to variations in their Vd and Clearance. For example, in the case of patient 4, steady state C_{pmax} and C_{pmin} concentrations of 14.3mg/L and 4.4mg/L were observed following administration of 1g Vancomycin (dosage interval = 24 hours), while receiving CVVHDF therapy with a dialysis fluid rate of 2L/hr and an ultrafiltration rate of 2L/hr (actual achieved effluent flow rate was 4.05L/hr). In contrast, under the same technical CVVHDF conditions and the same vancomycin dosing schedule, C_{pmax} and C_{pmin} concentrations of 24.4mg and 7.0mg were observed in Patient 8 (8A). This variation in serum concentrations reflected a significantly higher

Vd in Patient 4, resulting in a higher clearance, although elimination rate constants were similar for both patient profiles.

4.3.8 CVVHDF Clearance of Vancomycin

Details of vancomycin and creatinine clearance by CVVHDF are given in Table 4.3.9. The mean clearance of vancomycin by CVVHDF (Cl_{CVVHDF}) was 2.1+/- 0.3 L/hr, which was 82 +/- 15% of the estimated TBC. For one patient profile (2C), all of the vancomycin eliminated was removed by CVVHDF. The mean creatinine clearance by CVVHDF was 2.25 +/- 0.26 L/hr (37.5 +/- 4.5ml/min), which corresponds to a moderate degree of renal impairment in a normal subject, not treated with CVVHDF. A suggestion for the difference between vancomycin clearance and creatinine clearance in patients with normal renal function has been that vancomycin may undergo renal tubular reabsorption; as this is not a possible explanation for the differences in clearances due to CVVHDF, perhaps it may be explained by significant protein binding of vancomycin. The average amount of vancomycin removed by CVVHDF in a dosage interval (18-24 hours) was 755 +/- 142mg.

Table 4.3.9: Clearance of Vancomycin and Creatinine by CVVHDF

Patient Profile	Cl_{CVVHDF} (L/hr)	Cl_{CREAT} (L/hr)	F_{CVVHDF} (%)	A_{CVVHDF} (mg)	Measured 'effluent fluid' rate (L/hr)	Prescribed 'effluent' flow rate (L/hr)
1A	2.2	2.2	0.73	740	3.2	3.0
2C	1.8	1.9	1.00	987	2.9	3.0
3A	2.3	2.4	0.79	639	3.3	4.0
5C	1.7	2.0	0.95	802	2.4	3.0
6A	2.6	2.5	0.87	809	4.1	4.0
7C	2.1	2.3	0.91	887	3.0	3.0
8B	2.2	2.4	0.73	614	3.1	3.0
9B	2.4	2.4	0.65	709	2.9	3.0
10C	2.1	2.2	0.53	504	3.1	3.0
11D	1.6	1.8	0.95	911	2.8	3.0
12C	2.5	2.7	0.89	703	3.6	4.0

Cl_{CVVHDF}: Clearance of Vancomycin through the filter
Cl_{CREAT}: Clearance of Creatinine through the filter
F_{CVVHDF}: Fraction of TBC due to CVVHDF while operating
A_{CVVHDF}: Amount of Vancomycin removed by CVVHDF in dosing interval

The mean (+/- SD) serum vancomycin concentration and effluent fluid (ultrafiltrate/dialysate) concentration data are displayed in Table 4.3.10. There was no detectable difference in the performances of the filter in clearing vancomycin or creatinine over each 2 hour interval of the study. The measured sieving coefficient for vancomycin (S_{vanco}) was 0.73 +/- 0.14. The highest sieving coefficient was observed in a patient with profound hypoalbuminaemia (S.C. = 0.83 in patient 9) and the lowest in a patient with coagulopathy (S.C. = 0.57 in patient 11). Estimations of the clearance of vancomycin by CVVHDF

using S.C. values and the measured effluent fluid flow rates agreed well with the directly measured values. The mean estimated clearance of vancomycin using the estimated S_{vanco} was 2.3 +/- 0.4 L/hr. For many patients (n=10), there was a discrepancy between the intended, prescribed dialysate/ultrafiltrate flow rates and the actual flow rates achieved. The mean effluent flow rate prescribed was 3.3 +/- 0.5 L/hr versus the mean flow rate achieved of 3.1 +/- 0.4 L/hr. This is a potential source of error when estimating vancomycin clearance (Cl_{CVVHDF}) using the product of the S.C. and the prescribed flow rates, rather than the measured flow rates. Based on the data in this study, the use of this approach (Cl = Q X S.C.) would have led to a slight overestimation of vancomycin clearance by the filter compared to the directly measured Cl_{CVVHDF} (2.4 L/hr vs. 2.1 L/hr).

The sieving coefficient for creatinine was 0.79 +/- 0.07. Creatinine clearance by CVVHDF may be used as an approximate indicator of vancomycin elimination but slightly overestimates vancomycin clearance. The sieving coefficient is an indicator of the permeability of the haemofilter to the drug under investigation. Fig. 4.3.3 displays mean serum and effluent fluid Vancomycin concentrations over a single dosage interval. The ratio between serum and ultrafiltrate concentrations indicates the sieving coefficient.

Table 4.3.10: Mean (+/- SD) serum and effluent fluid vancomycin concentrations during CVVHDF

Time (hours)	Serum concentration (mg/L)	Effluent fluid Concentration (mg/L)
1	26.8 +/- 6.4	19.3 +/- 5.8
3	23.8 +/- 5.7	17.1 +/- 4.1
6	19.9 +/- 4.8	14.5 +/- 4.4
9	16.7 +/- 5.1	12.2 +/- 4.5
12	13.9 +/- 4.9	10.2 +/- 4.0
18	11.6 +/- 4.0	8.1 +/- 3.8
24	10.2 +/- 4.2	7.6 +/- 3.0

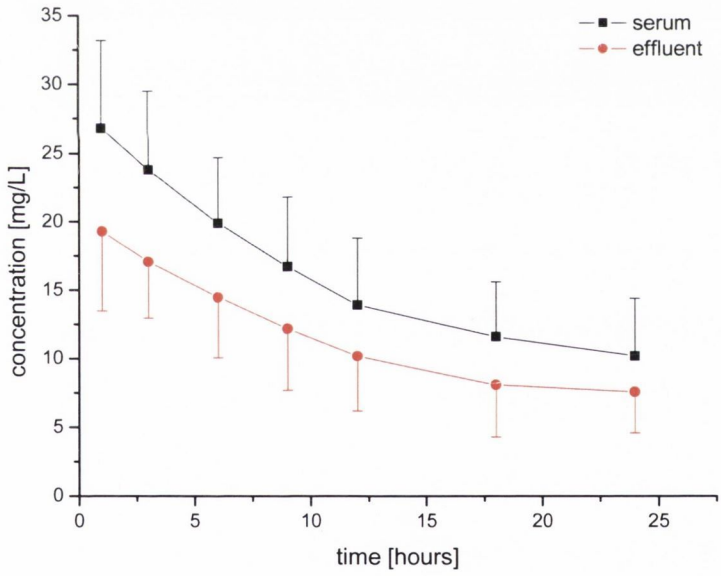


Figure 4.3.3: Plot of Vancomycin Serum and Effluent fluid (ultrafiltrate/dialysate) concentrations over time during CVVHDF.

4.4 Vancomycin Dosing during CVVHDF

Given the level of inter and intra-patient variability in vancomycin pharmacokinetics during CVVHDF, dosage adjustment should be made on the basis of serum concentrations as early as possible in drug therapy. PK-PD goals should be established on the basis of sensitivity data. Subsequently, target C_{pmax} and C_{pmin} concentrations together with estimates of individualised pharmacokinetic parameters should be used to design the optimum dosing schedule. On the basis of the pharmacokinetic parameters estimated in this study, a 1g dose at intervals of 18-24 hours, depending on PK-PD goals and individualised PK parameters seems appropriate. Monitoring of creatinine concentrations in effluent fluid, with careful measurement of collected effluent volumes over a defined time period can be used to obtain an accurate estimate of vancomycin clearance by CVVHDF.

Chapter 5: Aminoglycoside Pharmacokinetics during CVVHDF

5.1 Introduction

5.1.1 Aminoglycoside Antibiotics: Mechanism of Action and Antimicrobial Activity

Aminoglycosides are bactericidal antibiotics used in the management of serious gram-negative systemic infections in the critically ill patient and are used in the empirical treatment of gram-negative sepsis, for the management of serious Pseudomonas aeruginosa infections, and as supportive agents in the treatment of endocarditis.

Their mechanism of action involves binding to the 30S ribosome and inhibiting bacterial protein synthesis (156). Aminoglycosides diffuse through aqueous channels formed by porin proteins in the outer membrane of gram negative bacteria and enter the periplasmic space (157). Subsequent transport of aminoglycosides across the cytoplasmic (inner) membrane is dependent on electron transport, in part because of a requirement for a membrane potential (interior negative) to drive permeation of these antibiotics (158). This phase of transport is rate-limiting and can be blocked or inhibited by divalent cations, hyperosmolarity, a reduction in pH and anaerobiasis. Thus, for example, the antimicrobial effect of aminoglycosides is reduced in the anaerobic environment of an abscess and in hyperosmolar acidic urine (158).Following transport across the cytoplasmic membrane; the aminoglycosides bind to polysomes and interfere with protein synthesis by causing misreading and premature termination of translation of mRNA. The aberrant proteins produced may be inserted into the cell membrane, leading to altered permeability and further stimulation of aminoglycoside transport (159).

Bacteria may be resistant to the antimicrobial activity of the aminoglycosides because of failure of permeation of the antibiotic, low affinity of the drug for the bacterial ribosome, or inactivation of the drug by microbial enzymes. The latter mechanism is by far the most important explanation for the acquired microbial resistance to aminoglycosides that is encountered in clinical practice. Plasmid-mediated elaboration of aminoglycoside-inactivating enzymes has become a source of concern with regard to treatment of enterococcal infections. In several centres, a significant percentage of clinical isolates of these organisms are highly resistant to all aminoglycosides because of this mechanism (160). The synergistic bactericidal effect of certain beta-lactam antibiotics and vancomycin in combination with aminoglycosides on enterococci is lost. An additional complicating factor is the ability of enterococci to acquire plasmids that code for beta-lactamases (161) and vancomycin reistance (162). These factors could make serious enterococcal infections, such as endocarditis, extremely difficult to treat.

Aminoglycosides have bactericidal activity against most gram-negative bacteria including Acinetobacter, Citrobacter, Enterobacter, E. coli, Klebsiella, Proteus, Providencia, Pseudomonas, Salmonella, Serratia, Shigella. The MICs of gram negative bacteria are usually less than 2-4 micrograms/ml for gentamicin and 8 micrograms/ml for amikacin (163). Aminoglycosides are effective against most strains of Staphylococcus aureus and Staph. epidermidis. Most strains of enterococcus are resistant to aminoglycosides alone, however when used in combination with penicillins they are often effective in enterococcal endocarditis due to synergistic antimicrobial mechanisms. With the exception of streptomycin, all aminoglycosides have good activity against gram-negative aerobic bacilli but lack activity against anaerobes. Gentamicin,

amikacin, tobramycin and netilimicin are used in the treatment of serious gram-negative bacillary infection.

Gentamicin and tobramycin display similar antibiotic activity against gram-negative bacilli with two differences; tobramycin is more active against P. aeruginosa and gentamicin is more active against Serratia marcescens (164). Resistance of gram-negative bacilli to gentamicin and tobramycin has been reported (160). This resistance is most commonly due to a plasmid-mediated enzymatic alteration of the aminoglycoside. Amikacin has the same spectrum of activity as gentamicin but is less susceptible to enzymatic inactivation. Therefore, amikacin is valuable in treating gram-negative bacilli resistant to gentamicin (165).

5.1.2 Toxicity

A disadvantage of the aminoglycosides is their association with nephrotoxicity and ototoxicity. The reported incidence of nephrotoxicity varies substantially between studies, averaging 6% to 10% (166-171). Factors associated with nephrotoxicity include duration of treatment, renal insufficiency, volume depletion, increasing age, elevated trough concentrations and prolonged high peak levels, concurrent nephrotoxic drugs and previous exposure to aminoglycosides. Two large randomised controlled trials have reported a significantly higher percentage of nephrotoxicity in patients treated with gentamicin than in those treated with amikacin, 8% versus 0% respectively, and 20% versus 6% respectively (172,173). As the incidence of nephrotoxicity has varied substantially among different reports, it is difficult to assess either the absolute risk of toxicity or the relative differences in risk among aminoglycosides. Overt ototoxiciy generally occurs in 2-10% of patients treated with aminoglycosides (174). Gentamicin is more likely to produce

vestibular damage than hearing loss, whereas amikacin is more likely to produce hearing loss than vestibular damage (175-177). Vestibular damage from streptomycin is common with prolonged use and in patients with renal impairment. The 8^{TH} nerve toxicity is irreversible and is more likely to occur with higher doses and elevated blood concentrations, longer duration of therapy, in elderly patients, with renal impairment, with pre-existing hearing problems/underlying disease states and in those receiving concurrent ototoxic drugs and with previous exposure to aminoglycosides (175-177). Variability in the incidence of these adverse effects in patients treated with aminoglycosides may be partially explained by differences in populations, different methods of drug administration and duration of use.

Recent insight into their pharmacodynamic properties (PD) has led to a significant change in dosing practices in the last decade. Extended-interval dosing has now become the standard in most clinical settings, based on the theory and clinical evidence of efficacy and toxicity (178-181).

5.1.3 Pharmacokinetic properties

Aminoglycosides are highly water-soluble, poorly lipid soluble compounds. They are poorly absorbed from the gastrointestinal tract and must be given parenterally for the treatment of systemic infections. The IV route is the primary route of administration but they are occasionally given IM. Aminoglycosides are rapidly absorbed after IM administration; however, in patients older than 40 years, there is more interpatient variability (182). In critically ill patients, particularly patients with sepsis, intramuscular absorption can be reduced due to decreased blood perfusion to the intramuscular site and so the intravenous route is generally preferred. Amikacin and gentamicin demonstrate remarkably similar pharmacokinetics. Due to their polar nature,

the aminoglycosides are distributed mainly in the extracellular fluid (approx. 25% body weight). Protein binding is low (20-30%) and is generally not clinically significant. Vds are low, consistent with the distribution of the drug into extracellular water. The Vd is generally around 0.25L/kg, although a wide range of 0.06 to 0.84 L/kg has been reported and co-morbidities must be considered (183). Interpatient variability in the Vd of aminoglycosides has been reported by several studies and an increased volume of distribution has been suggested in patients with congestive heart failure, peritonitis, ascites, oedema, pleural effusion, acute burn injury, AIDs, immediately post partum patients or in the perioperative period (184,185). There is also potential for intra-patient variability during therapy; for example patients who are initially dehydrated or fluid overloaded at the start of therapy will experience respective increases and decreases in Vd with subsequent treatment (186). These changes may have a significant effect on serum concentrations and dosage requirements. Additionally, changes in the patient's cardiovascular haemodynamics and the extracellular fluid compartment may change the drug's clearance and distribution volume. For example, in a patient with oedema and fluid overload, the cardiac output, renal blood flow, glomerular filtration and drug clearance may increase, provided the CVS can tolerate the fluid load (186).

Penetration to several body fluids including peritoneal, ascitic, pleural fluids and synovial fluid is good, but poor into the central nervous system and the vitreous (187,188). Aminoglycosides must be given intrathecally for CNS infections and periocular/intraocular injections are required for bacterial endophthalmitis (189). High concentrations are found in the renal cortex (190,191,192,193) and in the endolymph and perilymph of the inner ear

(194,195), which may explain the nephrotoxicity and ototoxicity associated with these drugs. Since aminoglycosides distribute very poorly into adipose tissue, lean rather than total body weight (TBW) should result in a more accurate estimate of Vd in obese patients. The aminoglycoside Vd in obese patients could also be adjusted on the basis of the patient's ideal body weight (IBW) plus 10% of his or her excess weight.

Vd(obese) = (0.25L/kg)(IBW) + 0.1(TBW-IBW). (Equation 5.1.1)

IBW (males in kg) = 50 + (2.3)(Height in inches > 60) (Equation 5.1.2)

IBW (females in kg) = 45 + (2.3)(Height in inches > 60) (Equation 5.1.3)

As an increased volume of distribution can be anticipated for patients with oedema or ascites and this may impact on dosage requirements, it is helpful to approximate the increased volume of distribution for these patients. One approach suggested by Winter is to increase the distribution volume for 1L for each kg of weight gain (196). Clearly, this approach assumes that the volume of distribution of aminoglycosides approximates extracellular fluid volume and requires regular measurements of the patient's weight.

Aminoglycoside Volume of Distribution (L) =

(0.25L/kg x non-obese, non-excess fluid weight (kg))

+ 0.1 (excess adipose weight (kg)) + (Excess 'fluid overload' weight (kg)).

(Equation 5.1.4)

Aminoglycosides are primarily eliminated by the kidneys unchanged by glomerular filtration with some active secretion. Active reabsorption by the proximal tubule is a factor in their nephrotoxicity. Elimination by the renal route accounts for 85-95% of the administered dose and a small amount of drug excretion in bile has been suggested as an additional route of elimination (195). Aminoglycoside clearance is approximated by creatinine clearance,

when concentrations are within the therapeutic range, for example, as estimated by the Cockcroft and Gault equation (1.5.3.4 and 1.5.3.5). Correct estimates of creatinine clearance can only be obtained if the patient's weight represents a normal ratio of muscle mass to total body weight and the serum creatinine is at steady state. For critically ill patients, particularly with acute renal failure, rapid changes in renal function often make this difficult. Adjustments for obesity and altered fluid volume must be considered and there is potential for 'dilution' of serum creatinine concentrations by a large volume of distribution. In healthy volunteers, 80-90% of the variance in elimination of aminoglycosides is explained by renal function (197). However, this relationship changes markedly among critically ill patients. Barza et al (179) reported that only 52% of the variation in gentamicin elimination could be explained by changes in the serum creatinine for a group of patients with sepsis. Kaye et al (194) reported a similar finding with only 50% of the variation in gentamicin clearance explained by a change in creatinine clearance in a group of critically ill patients. For amikacin, only 46% of the variation in its half-life was explained by a change in serum creatinine.

Both amikacin and gentamicin display remarkably similar pharmacokinetics and the elimination rate constants are approximately 2-3 hours in patients with normal renal function. In patients with renal insufficiency and the elderly, the half-life increases markedly and dosage reduction is required to avoid accumulation and toxicity. The non-renal clearance of aminoglycosides, although largely ignored in patients with normal renal function, may become significant in patients with renal insufficiency. For functionally anephric patients, on intermittent haemodialysis, a nonrenal clearance of 5ml/min/70kg has been suggested (199). However, serum concentration monitoring of

aminoglycosides should be the primary guide of dosing schedule design in patients with impaired renal function.

5.1.4 Therapeutic Range and Pharmacodynamic Properties

Target therapeutic ranges depend on putative organism and site of infection and the dosing schedule in use; either conventional multiple daily doses ('tds dosing') or once-daily (extended interval) dosing.

Aminoglycosides exhibit concentration-dependent killing of gram-negative bacteria: the higher the concentration, the greater the rate at which bacteria are killed (200,201). A postantibiotic effect, that is residual bactericidal activity persisting after the serum concentration has fallen below the MIC is characteristic of aminoglycoside antibiotics and the duration of this effect is concentration-dependent. Studies (202 – 207) that have examined the ratios of aminoglycoside concentration to MIC and area under the curve (AUC) to MIC have established that aminoglycoside concentration is a more important factor than time above the MIC in determining the pharmacodynamic effect of bacterial killing with these agents.

Optimal patient outcomes and suppression of resistance emergence are associated with a peak concentration/MIC ratio of at least 8:1 to 10:1 (203,204). There is also strong evidence suggesting that the first dose of an aminoglycoside is the most important in the course of therapy (204). Adaptive resistance is a phenomenon in which bacteria exhibit down-regulation of drug uptake upon frequent and repeated exposures to antimicrobial agents. Consequently, the first dose of aminoglycoside has the most bactericidal effect on the bacteria population. It has also been reported that attainment of a pharmacodynamic target (Cmax/MIC>10) within 48 hours of therapy is associated with an early therapeutic response (203,204). Since the likelihood of

aminoglycoside-induced nephrotoxicity is believed to be dependent on the cumulative drug exposure and/or concentration above a certain threshold, achieving a pharmacodynamic target early may shorten the duration of therapy and thus reduce the likelihood of drug-induced adverse effects (205,207,208). As aminoglycosides exhibit concentration-dependent killing, peak concentrations (C_{pmax}) and C_{pmax}/MIC rations have been suggested as the best predictors of therapeutic efficacy. Thus, the goal of therapy is to maximise 'peak' concentrations while avoiding toxicity and excessive accumulation. This can be best achieved through administering high doses at extended intervals. Peak and trough aminoglycoside serum concentrations should be monitored in order to estimate pharmacokinetic parameters for dosage individualisation and to assess the efficacy of existing dosing regimens, in achieving adequate C_{pmax}/MIC ratios, while avoiding toxicity. In this hospital, target peak and trough plasma concentrations using extended interval dosing are >50 mg/L and <5mg/L respectively and these criteria are consistent with literature ranges of 40 – 60 mg/L and <5mg/L (209-211). Most available data correlating aminoglycoside concentrations with ototoxicity and nephrotoxicity refer to trough serum concentrations or prolonged high serum concentrations. Continuous infusions would appear to have the highest risk of toxicity and extended interval dosing has been associated with a lower level of toxicity than conventional multiple daily dosing (212). Low peak serum aminoglycoside concentrations are associated with an increased risk of clinical failure and the emergence of resistant strains. A marked variability in aminoglycoside pharmacokinetic parameters has been reported in critically ill patients (213,214,215).

5.1.5 Pharmacokinetic Models

The pharmacokinetics of the aminoglycoside antibiotics have been described by a two-or three- compartment model (191, 216). However, a one-compartment model has been widely used in the clinical setting to facilitate aminoglycoside pharmacokinetic calculations (217-224). Although, additional samples will provide more information describing the concentration-time curve, the amount of additional information decreases markedly after three or four samples. When given by IV infusion over 30 minutes, aminoglycosides follow a 3-compartment pharmacokinetic model; alpha (distribution), ß (elimination), and gamma (tissue release). When infused over one hour, the distribution phase is usually not observed. The gamma phase begins approximately sixteen hours post infusion, drug that was tissue bound to various organs is released. The amount released from tissue is very small, but does accumulate over time, contributing to aminoglycoside toxicity. A one-compartment model provides a clinically useful framework for estimating the serum level time curve of aminoglycosides. Two parameters are required for this model, apparent volume of distribution (Vd) and elimination rate (k_{el}). For initial dosing, before serum level data are available, the elimination rate can be estimated from a Dettli plot of Cl_{cr} versus k_{el} in patients with stable renal function.

$$k_{el} = 0.01 + (Cl_{cr} \times 0.0024) \qquad \text{(Equation 5.1.5)}$$

The apparent volume of distribution can be estimated by multiplying a population average by the patient's weight. The Vd varies considerably between patients, and this variability has a substantial effect on serum concentrations and dosage requirements. Dosage regimens necessary to achieve therapeutic aminoglycoside serum concentrations can be quantitatively

determined by using simple pharmacokinetic principles. Individualized pharmacokinetic parameters are determined from the patient's serum concentration versus time data. Sawchuk and Zaske (4) have described a method for establishing multiple infusion regimens based on individually calculated pharmacokinetic parameters. Although a two- or three- compartment model can be used to accurately represent the time course of aminoglycoside serum levels, it cannot be used clinically because of its complexity. Therefore, the simpler one compartment model is widely used, and allows accurate prediction of aminoglycoside levels and clinically useful estimates of drug disposition for aminoglycosides.

5.1.6 Aminoglycoside pharmacokinetics during Renal Replacement Therapy (RRT)

A marked variability in aminoglycoside pharmacokinetic parameters has been reported in critically ill patients. Sepsis and Total Parenteral Nutrition (TPN) have been associated with an increased volume of distribution for aminoglycoside antibiotics (214,221).

As aminoglycosides are primarily eliminated via the renal route, have a low level of protein binding and low molecular weight, they are likely to be cleared by CVVHDF. Prior to the commencement of this study, dosage of aminoglycosides was calculated during CVVHDF, on the basis of the patient's renal dysfunction. The preliminary audit demonstrated an increase in the use of amikacin during CVVHDF therapy. There is currently very little data in the literature describing amikacin pharmacokinetics during RRT. One study (n=4 patients) (222) demonstrated a significant difference in amikacin clearance between intermittent haemofiltration in comparison with haemodialysis and peritoneal dialysis but did not investigate clearance by CVVHDF. The use of

intermittent haemofiltration rather than CVVHDF and major differences in the patient case mix (stable, ESRD patients) makes comparisons with our patient sample difficult. A report (223) of amikacin pharmacokinetics during CVVH also concluded that amikacin clearance was enhanced by CVVH. In contrast, a further report of one patient (224) stated that there was no alteration of the half-life of amikacin during CVVH and concluded that clearance during CVVH is similar to that in patients with renal failure who are not being treated with CVVH.

There is a similar absence of data for gentamicin; a report (225) of gentamicin elimination in a single patient undergoing CAVU observed a half-life of 65.4 hours. As clearances are far lower with CAVU than with CVVHDF, a much shorter half-life would be anticipated. Such confounding reports of amikacin behaviour during earlier forms of CRRT, together with the deficit of data on aminoglycoside pharmacokinetics during CVVHDF, formed the impetus for this study.

5.2 Retrospective Pharmacokinetic Evaluation of Amikacin in Critically Ill Patients during CVVHDF therapy.

5.2.1. Introduction

The previous chapter demonstrated that routine TDM data can be used successfully to determine individual patient pharmacokinetic parameters for patients treated with CVVHDF. The aminoglycoside antibiotics, amikacin and gentamicin, are drugs for which such serum concentration data are routinely measured. The audit, described in Chapter 3, showed that these antimicrobial agents are sometimes used for patients treated with CVVHDF. The objective of this chapter was to investigate such data and in so doing to assess the impact of CVVHDF on aminoglycoside pharmacokinetics during CVVHDF therapy, with the ultimate aim of dosage optimisation.

5.2.2 Patients

Of the eight patients examined, there was adequate data available for five patients for their inclusion in the analysis. Patients whose CVVHDF therapy was interrupted while receiving amikacin (n=2), or where the required minimum of two serum drug concentrations for a dosage interval were absent (n=1), were not included in the study. The patient population was described by recording age, sex, serum creatinine, Acute Physiology and Chronic Health Evaluation (APACHE) II score, maximum Sequential Organ Failure Assessment (SOFA) score, admitting diagnosis and microbiological infection. Accurate weight measurements were unavailable due to the clinical status of these patients, who were unconscious or sedated. Clinical and demographic data are tabulated below (Table 5.2.1). Four men and one woman successively treated with amikacin during CVVHDF therapy, ages 40-75 years (mean: 54 years) were included in the analysis. One patient with persistent pyrexia and a

raised WCC was treated empirically for suspected sepsis. Acinetobacter baumanni was isolated in wound swabs for two patients. Amikacin was prescribed to treat gram-negative bacillus (patient 2), pseudomonas aeruginosa (patients 3 and 4) and escherichia coli (patient 5). Patient 1 had diagnosed preexisting renal impairment on admission. All patients had ARF on commencing CVVHDF therapy and remained anuric throughout. Four patients had persistent oedema and two had ascites. Four patients had concomitant hepatic impairment. Four patients had concurrent gram-positive infection. The mean APACHE Π score was 22.8 +/- 4.0 and the mean SOFA score was 8.2 +/- 2.0. The mean duration of CVVHDF was 16 days. Access to the circulation had been established through the subclavian femoral internal jugular vein. A 0.6 m^2 polyacrilonitrile cylinder haemofilter (Prisma M100, Preset AN69HF, Hospal, Lyon, France) was connected after heparinised saline priming. CVVHDF was run heparin-free in the case of Patient 1, due to coagulopathy. Blood was pumped through the membrane at a rate of 200ml/min. The dialysate fluid passed once across the membrane into the dialysate compartment of the filter at a rate of 1L/hr for patients 1, 3 and 5. For patients 2 and 4 CVVHDF was performed with 2 L/hr dialysate and 2 L/hr pre-dilution filtration solution, producing 4L/hr dialysis effluent. Details for individual patients are presented in Tables 5.2.2.

Table 5.2.1: Patient Demographics and Clinical Characteristics of Critically Ill Patients treated with CVVHDF and Amikacin.

ID	Sex	Age	Diagnosis	Infective Diagnosis	APACHE II score[1]	SOFA score[2]	SrCr[3]	Cr Cl[4]	Duration of CVVHDF (days)
1	M	56	Multiple myeloma, acute and chronic renal failure, acidosis, severe oedema, coagulopathy	Empiric cover for suspected sepsis	30	7	188	6	17
2	F	54	ARF secondary to rhabdomyolysis, acute hepatic impairment, acidosis	Acinetobacter baumanii, Gram negative bacillus,coagulase negative staphylococci	31	8	755	1	15
3	M	40	Pancreatitis, ARF, ATN, sepsis, SIRS, acidosis, oedema	Actinetobacter baumanni, Enterococcus Faecalis, Pseudomonas aeruginosa,Coagulase negative staphylococci	18	7	167	7	15
4	M	75	Postrenal failure, Small bowel obstruction, ascites	Enterococcus faecalis, Pseudomonas aeruginosa, MRSA	23	5	161	4	9
5	M	45	Chronic active autoimmune hepatitis (30yrs), ascites, hepatic failure, oesophageal varices, portal HTN, strep. mitis endocarditis	Gram positive cocci, Escherichia coli, Enterococcus faecalis, Enterococcus faecium.	29	9	264	2	24

[1] Initial/ICU admission value

[2]Initial/ICU admission value

[3]Value on day 1 of CVVHDF therapy, prior to commencing CVVHDF. Units = μmol/L.

[4] Value on day 1 of CVVHDF therapy, prior to commencing CVVHDF, estimated using the method of Jeliffe and Jeliffe (42). Units = ml/min.

5.2.3 Pharmacokinetic Analysis

Details of dosing schedules and estimated pharmacokinetic parameters for each patient are given in Table 5.2.2.

Table 5.2.2: Individual patient estimates of amikacin pharmacokinetic parameters during treatment with CVVHDF (1-compartment model).

Patient Profile	UF Rate (L/hr)	Dose (mg)	τ (hrs)	Cpmax (mg/L)	Cpmin (mg/L)	$T_{1/2}$ (hrs)	k (hr^{-1})	TBC (L/hr)	Vd (L)
1A	1.9	500	24	12.8	2.8	10.94	0.063	2.975	47.23
1B	2.0	500	23	19.9	2.4	7.53	0.092	2.555	27.77
1C	2.0	500	23	21.9	2.6	7.47	0.093	2.364	25.42
1D	2.0	500	24	20.4	3.1	8.82	0.079	2.223	28.14
1E	2.0	500	24	16.5	3.3	9.90	0.070	2.540	35.97
Mean						**8.93**	**0.079**	**2.531**	**32.91**
stopped									
1F	N/A	*500*	*24*	*17.8*	*9.5*	*26.48*	*0.026*	*1.534*	*52.48*
1G	N/A	*650*	*30*	*30.6*	*17.3*	*36.45*	*0.019*	*0.637*	*33.50*
1H	N/A	*650*	*30*	*37.8*	*19.9*	*32.40*	*0.021*	*0.718*	*34.19*
2A	2.0	500	24	14.5	1.4	7.11	0.097	3.632	37.44
2B	2.0	500	24	19	1.4	6.38	0.109	2.999	27.51
2C	2.0	550	22	18.6	1.5	6.05	0.114	3.545	31.11
2D	2.0	700	22	19.1	2.6	7.64	0.091	3.640	40.01
2E	2.0	800	22	24.6	3.8	8.16	0.084	3.139	37.37
2F	2.0	800	22	28.6	3.7	7.45	0.093	2.816	30.28
2G	2.0	800	24	28.4	2.9	7.29	0.095	2.795	29.42
Mean						**7.15**	**0.098**	**3.224**	**33.31**
3A	1.9	400	24	19.9	1.5	6.43	0.108	2.220	20.56
3B	2.0	400	24	14.3	2.0	8.46	0.082	2.568	31.32
3C	2.0	600	24	29.3	2.1	6.31	0.110	2.276	20.69
3D	2.0	600	24	21.2	2.7	8.07	0.086	2.640	30.70
3E	2.0	550	24	17.6	2.6	8.70	0.080	2.782	34.78
3F	2.0	550	16	25.0	8.6	10.40	0.067	2.108	31.47
3G	1.8	600	24	33.6	4.8	8.55	0.081	1.601	19.76
3H	1.8	600	24	27.6	2.6	7.04	0.098	2.221	22.66
Mean						**7.99**	**0.089**	**2.302**	**26.49**
4A	2.0	300	24	7.4	1	8.31	0.083	3.657	44.06
4B	2.0	200	24	10.4	1	7.10	0.098	1.959	19.99
4C	2.0	350	24	11.7	1.2	7.30	0.095	2.970	31.26
4D	2.0	350	24	13.2	1.7	8.11	0.085	2.143	25.22
4E	2.0	350	24	11.2	1.1	8.87	0.078	3.343	42.86
4F	1.8	350	24	17.6	1.7	7.12	0.097	2.014	20.76
4G	1.8	500	24	17.7	2.1	7.80	0.089	2.693	30.26
4H	2.0	500	24	20.5	3.0	8.66	0.080	2.169	27.11
Mean						**7.91**	**0.088**	**2.619**	**30.19**
5A	2.0	320	24	13.2	1.6	7.88	0.088	2.361	26.82
5B	2.0	400	26	13.6	1.5	8.29	0.084	2.707	32.23
5C	2.0	600	24	N/A	2.9	N/A	N/A	N/A	N/A
5D	2.0	800	24	20.2	3.6	9.64	0.072	3.275	45.49
5E	2.0	1000	24	31.3	4.8	8.87	0.078	2.792	35.80
5F	2.0	900	24	25.9	5.1	10.23	0.068	2.798	41.14
Mean						**8.98**	**0.078**	**2.787**	**36.30**

The mean number of pharmacokinetic data sets per patient was 7.2. In the case of one patient, it was possible to estimate amikacin pharmacokinetic parameters both during and following the discontinuation of CVVHDF. The serum concentration-time data for this patient, Patient 1, are presented below in Figure 5.2.1.

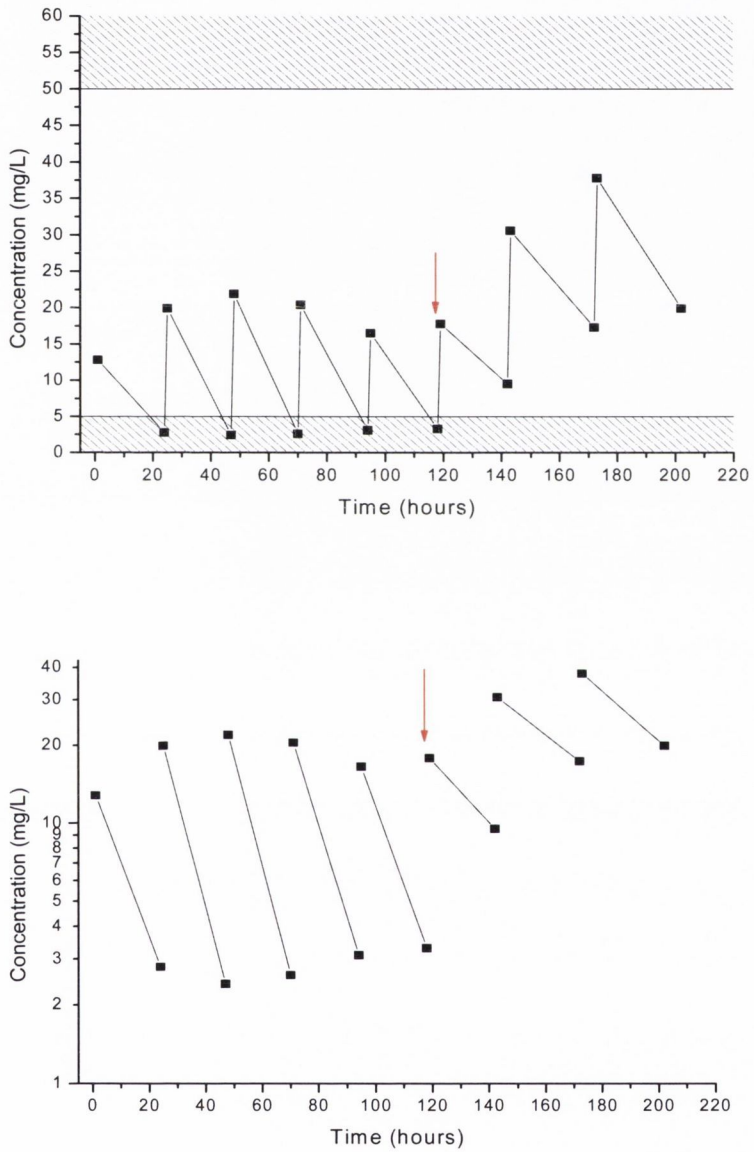


Fig.5.2.1: Linear and semi-log plots of amikacin peak and trough serum concentrations over time for patient 1. (Arrow indicates the time point at which CVVHDF was discontinued)

The range of doses administered, among this patient sample, was 200mg – 1000 mg. The dosage intervals used ranged from 16-24 hours during treatment with CVVHDF. In the patient where CVVHDF was stopped, while amikacin therapy continued, the dosage interval was increased to 30 hours. Figure 5.2.1 illustrates the impact of CVVHDF therapy on amikacin elimination. Amikacin 500mg was administered once daily to this patient. During CVVHDF therapy, this dosage regimen failed to achieve therapeutic serum concentrations. The mean peak concentration produced by this regimen during treatment with CVVHDF was 18.2 mg/L, less than half the target peak concentration. The mean trough concentration was 3mg/L. The mean (steady-state) amikacin half-life estimate for this patient during CVVHDF was 8.9 hours. The mean Vd estimate at steady state was 32.9 L. Following discontinuation of CVVHDF therapy, a more than 3-fold increase in the half-life was observed. The mean amikacin half-life estimate, following discontinuation of CVVHDF, was 31.8 hours. Unlike during CVVHDF therapy, accumulation was evident with once daily dosing when CVVHDF was stopped. In the case of patient 2, an initial dosage regimen of 500mg amikacin once daily resulted in subtherapeutic C_{pmax} concentrations. The dose was subsequently increased to 550mg, while the dosage interval was shortened to 22 hours. However, the C_{pmax} concentration remained far below the target concentration. Further dosage increases to 700mg and 800mg produced C_{pmax} serum concentrations that were approximately half the target concentration. Throughout the treatment period, all trough concentrations were less than 5mg, in accordance with target guidelines. The mean clearance estimate was 3.2 L/hr. The mean half-life estimate was 7.15 hours. The mean Vd estimate was 33.3L.

The starting dose for patient 3 was lower than for the two previous patients (400mg once daily). Subtherapeutic peak serum concentrations resulted (19.9mg/L and 14.3mg/L) and consequently higher doses followed. A dosage regimen of 600mg/24 hours increased peak concentrations (21.2mg/L – 29.3mg/L), but concentrations were still far lower than the target peak concentration. The target trough concentration was exceeded when the dosage interval was shortened to 16 hours and a 550mg dose resulted in a peak of 25mg/L and a trough of 8.6mg/L. The dosage regimen of 600mg every 24 hours was subsequently resumed and C_{pmin} concentrations returned to the target range (<5mg/L), while peak concentrations increased to some extent but remained less than the C_{pmax} target. The mean half-life estimate was 7.9 hours. The mean clearance estimate was 2.3L/hr. A reduction in the ultrafiltration rate during profile 3G coincided with a decrease in the observed amikacin clearance. A lower Vd (19.8L) was also estimated for this profile and may relate to an improvement in the patient's clinical status (resolving oedema). Patient 4 received the lowest starting dose of amikacin 300mg once daily. This dose produced the lowest observed peak concentration (7.4mg/L). The dosage interval was maintained at 24 hours for the duration of amikacin therapy and all trough concentrations were within the target range (C_{pmin}<5mg/L). Dosage increases to 350mg and 500mg amikacin failed to achieve target C_{pmax} concentrations. The magnitude of the doses administered was in line with those used in renal impairment, where dose reduction is recommended to avoid accumulation. However, the capacity of CVVHDF for amikacin clearance was greater than had been anticipated and consequently the doses administered resulted in lower than anticipated amikacin serum concentrations. The mean amikacin clearance estimate during CVVHDF was 2.6L/hr. The mean half-life

estimate was 7.9 hours.

In the case of patient 5, initial low doses (320mg/400mg once daily), produced subtherapeutic C_{pmax} concentrations, while the CVVHDF cleared the amikacin to C_{pmax} concentrations within the target range. In response to these low serum concentrations, amikacin doses were increased, first to 600mg, then 800mg and finally 1000mg. Although the C_{pmax} serum concentrations remained less than the target of 50-60mg/L, the concentrations were significantly increased. As the final dose produced a C_{pmin} concentration just outside the target range, extension of the dosage interval may be advisable, to allow higher doses to be administered without accumulation. The observed Vd estimate (mean =36.3L) in this patient was very high and contributed to the inadequacy of doses in terms of producing target serum concentrations. This patient had sepsis and extreme oedema, which have been associated with an increased Vd for the aminoglycosides (19, 30). The mean half-life estimate during CVVHDF for this patient was 8.98 hours and the mean clearance estimate was 2.79 L/hr.

5.2.4 Impact of CVVHDF therapy on Amikacin Pharmacokinetics as assessed by an analysis of amikacin TDM data.

Among this patient sample, the mean (+/- s.d.) amikacin half-life estimate during CVVHDF therapy was 8.08 +/- 1.20 hours (range = 6.05-10.94 hours). Following the discontinuation of CVVHDF therapy in the case of patient 1, there was a dramatic increase in the half-life. The mean Vd estimate was 32.18 +/- 7.95 L (range=19.76L - 47.23L). The mean amikacin clearance estimate during CVVHDF was 2.71 +/- 0.52 L/hr. In the patient where CVVHDF was discontinued during amikacin therapy, the mean clearance decreased from 2.5 L/hr during CVVHDF to 0.963 L/hr on stopping CVVHDF. Amikacin serum concentrations were consistently below the target range in patients treated with concurrent CVVHDF.

5.3: Retrospective Pharmacokinetic Evaluation Of Gentamicin In Critically Ill Patients During Cvvhdf Therapy.

5.3.1 Patients

Of the five patients treated concurrently with CVVHDF and gentamicin, there was adequate data available for four patients for their inclusion in the analysis. In the case of the fifth patient, interruptions to CVVHDF therapy complicated the interpretation of gentamicin serum concentrations and so the data for this patient was excluded from the analysis. The patient population was described by recording age, sex, serum creatinine, Acute Physiology and Chronic Health Evaluation (APACHE) Π score, maximum Sequential Organ Failure Assessment score, admitting diagnosis and microbiological infection. Accurate weight measurements were unavailable due to the clinical status of these patients, who were unconscious or sedated. Clinical and demographic data are tabulated below (Table 5.3.1). Three women and one man successively treated with gentamicin during CVVHDF therapy, ages 43-75 years were examined. All patients had ARF and creatinine clearance was estimated using the Jeliffe and Jeliffe method. Two patients were anuric throughout CVVHDF therapy. The mean duration of CVVHDF was 11 days. Access to the circulation had been established through the subclavian femoral or internal jugular vein. A 0.6 m^2 polyacrilonitrile cylinder haemofilter (Prisma M100, Preset AN69HF, Hospal, Lyon, France) was connected after heparinised saline priming. Blood was pumped through the membrane at a rate of 200ml/min. The dialysate fluid passed once across the membrane into the dialysate compartment of the filter at a rate of 1L/hr for patients 1 and 2 and the prescribed ultrafiltration rate was 2 L/hr. For patients 3 and 4, CVVHDF was prescribed with 2 L/hr dialysate and 2 L/hr predilution filtration solution, producing 4L/hr dialysis effluent. Where

deviations from the prescribed flow rates were recorded in the nursing notes; these were noted. Details for individual patients are presented in Tables 5.3.2. Gentamicin was prescribed to treat documented gram-negative infection in all patients. Escherichia coli was isolated from blood cultures from two patients. One patient also had infection due to Pseudomonas aeruginosa. Klebsiella pneumoniae and Acinetobacter baumannii were isolated from two further patients. Two patients had concurrent gram-positive infection and one patient was MRSA positive. The mean APACHE Π score was 28.3 +/- 2.8 and the mean SOFA score was 6.4 +/- 1.4.

Table 5.3.1: Patient Demographics and Clinical Characteristics of Patients prescribed Gentamicin during CVVHDF therapy

ID	Sex	Age years	Diagnosis	Infective Diagnosis	APACHE Π score[1]	SOFA Score[2]	SrCr[3] μmol	CrCl[4] ml/min	CVVHDF Duration (days)
1	F	75	Small bowel obstruction, post-op laparotomy, and resection.	E.coli, Coagulase negative staphylococci, Acinetobacter baumannii	25	4	92	6	9
2	F	43	Acute on chronic renal failure, anuric, decompensated alcoholic liver disease, ascites, vasculitis.	Klebsiella pneumoniae	30	7	737	1	11
3	M	70	Postrenal failure, Small bowel obstruction, ascites, oedema	Enterococcus faecalis, Pseudomonas aeruginosa, MRSA	31	7	161	3	8
4	F	61	Acute on chronic renal insufficiency, anuric, hypertension, A.fib., acidotic	E.coli, Pseudomonas aeruginosa	27	6	418	2	15

[1] Initial/ICU admission value

[2] Initial/ICU admission value

[3] Value on day 1 of CVVHDF, prior to commencing CVVHDF therapy. Units = μmol/L

[4] Value on day 1 of CVVHDF, prior to commencing CVVHDF therapy. Units = ml/min. Estimated using the method of Jelliffe and Jelliffe (42).

5.3.2. Pharmacokinetic Analysis of Gentamicin 'peak' and trough serum concentrations

Pharmacokinetic parameters, estimated from serum-concentration time profiles of gentamicin in the four patients are shown in Table 5.3.2. The mean number of data sets per patient was 3.5.

Table 5.3.2 Estimates of Pharmacokinetic Parameters for Gentamicin in Critically Ill Patients treated with CVVHDF.

Patient Profile	UF Rate (L/hr)	Dose (mg)	T (hrs)	Cpmax (mg/L)	Cpmin (mg/L)	Half-life (hrs)	k (hr^{-1})	Cl (L/hr)	Vd (L)
		270	24	N/A	1.1				
1A	1.8	160	24	4.9	0.9	9.82	0.070	2.730	39.006
1B	1.8	240	28	6.7	1.0	10.19	0.068	2.799	41.156
1C	2.0	320	28	9.1	1.1	9.18	0.075	2.929	39.054
1D	1.8	400	24	15	1.8	10.16	0.068	2.017	29.662
1E	1.8	320	34	10.9	1.5	11.95	0.058	1.965	33.887
Mean						**10.26**	**0.068**	**2.488**	**36.553**
2A	2.0	200	24	7.9	0.8	7.26	0.095	2.690	28.318
2B	2.0	260	24	10.2	0.9	7.37	0.101	2.740	27.133
2C	2.0	280	24	14.1	1.1	6.52	0.106	2.212	20.868
2D	2.0	280	28	14.6	1.0	7.24	0.095	1.904	20.038
Mean						**7.10**	**0.099**	**2.387**	**24.089**
3A	2.2	240	24	6.8	1.1	9.12	0.076	3.119	41.034
3B	2.0	240	24	7.1	1.0	8.49	0.082	2.892	35.266
Mean						**8.81**	**0.079**	**3.006**	**38.150**
4A	2.4	240	24	6.4	0.7	7.52	0.092	3.765	40.926
4B	2.2	240	24	6.9	0.8	7.70	0.090	3.443	38.252
4C	2.2	260	24	7.1	0.9	8.05	0.086	3.507	40.784
Mean						**7.76**	**0.089**	**3.572**	**39.987**

The mean peak concentration was 9.12 +/- 3.34 mg/L (Range = 4.90 – 15.0 mg/L). This concentration is below the target peak concentration range for once daily dosing, which in this Hospital is 10-20 mg/L. The desired trough concentration in AMNCH is less than 2mg/L and all trough concentrations remained below this threshold concentration. The range of trough concentrations was 0.7mg/L to 1.8mg/L (mean = 1.0 mg/L).

The mean half-life for gentamicin during CVVHDF therapy was 8.61 +/- 1.52 hours (Range = 6.52 – 11.95 hours), which corresponds to an average elimination rate constant of 0.083 hr^{-1}. Gentamicin clearance ranged from 1.90

L/hr to 3.76 L/hr (mean = 2.765 l/hr). The mean estimated Vd was 33.96 +/- 7.50 L, which is higher than reported in normal subjects. The mean peak concentration achieved by an initial dose was 6.5mg/L. This is significant, given that high C_{pmax} concentrations early in aminoglycoside therapy have been correlated with positive patient outcomes. In the case of three of the four patients, initial doses were subsequently increased. However, the extent of the dosage adjustment was not sufficient to achieve therapeutic serum concentrations. Patient 1 was prescribed gentamicin for an infection due to escherichia coli. The serum concentration time data for this patient is depicted in Figure 5.3.1.

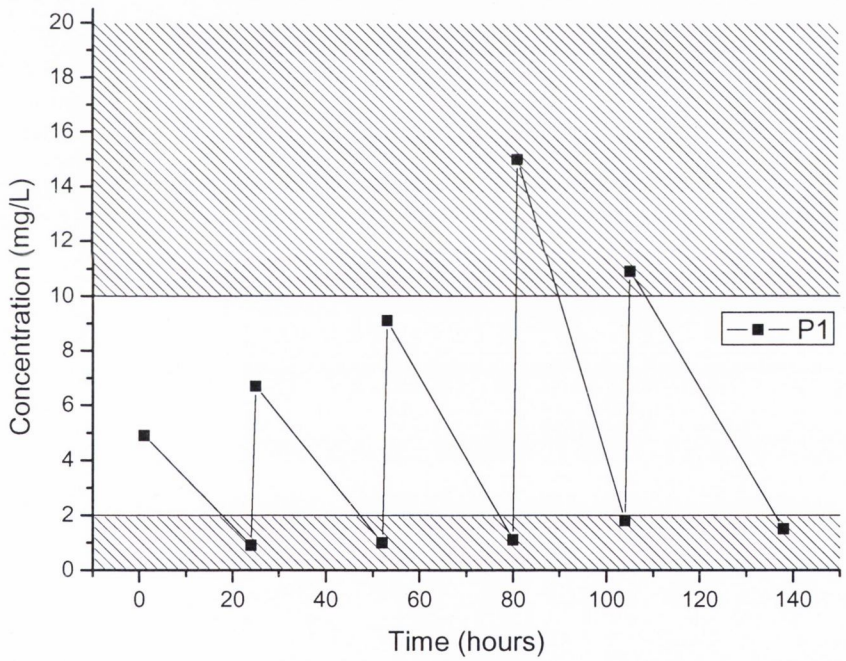


Figure 5.3.1: Gentamicin serum concentration-time data for Patient 1.

A doubling of the initial dose to 320mg remained inadequate in achieving a peak concentration within the target concentration range. A contributing factor to the low serum concentrations was the high observed Vd (mean = 36.55 L). A further dosage increase to 400mg achieved a C_{pmax} concentration within the general target range. Attaining an individualised pharmacodynamic goal, based

on an MIC for E.coli of 2mg/L and a target C_{pmax}/MIC of 10, would require a higher C_{pmax} of 20mg/L. The C_{pmin} concentration remained within the target range. Gentamicin-resistant Acinetobacter baumannii was isolated on the final day of gentamicin therapy and so therapy was discontinued. Previously, gentamicin-sensitive E. coli had been isolated. In the case of patient 2, gentamicin therapy was initiated to treat ciprofloxacin-resistant Klebsiella pneumoniae. Although, a starting dose of 200mg produced a subtherapeutic C_{pmax} concentration, subsequent dosage increases to 280mg resulted in serum concentrations that approached the therapeutic range. This is reflective of the lower Vd observed in this patient, which was in the normal range. Figure 5.3.2 depicts the serum concentration-time data for this patient.

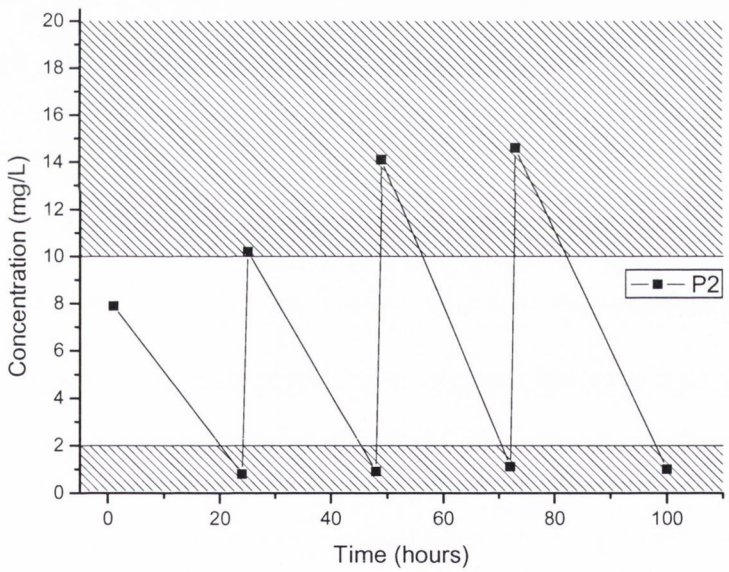


Figure 5.3.2: Gentamicin serum concentration time data for Patient 2.

An estimated mean clearance of 3L/hr and a high Vd of 38.15L were observed in Patient 3. The 240mg gentamicin dose did not attain target serum concentrations. Figure 5.3.3 presents the serum concencentration-time data for this patient.

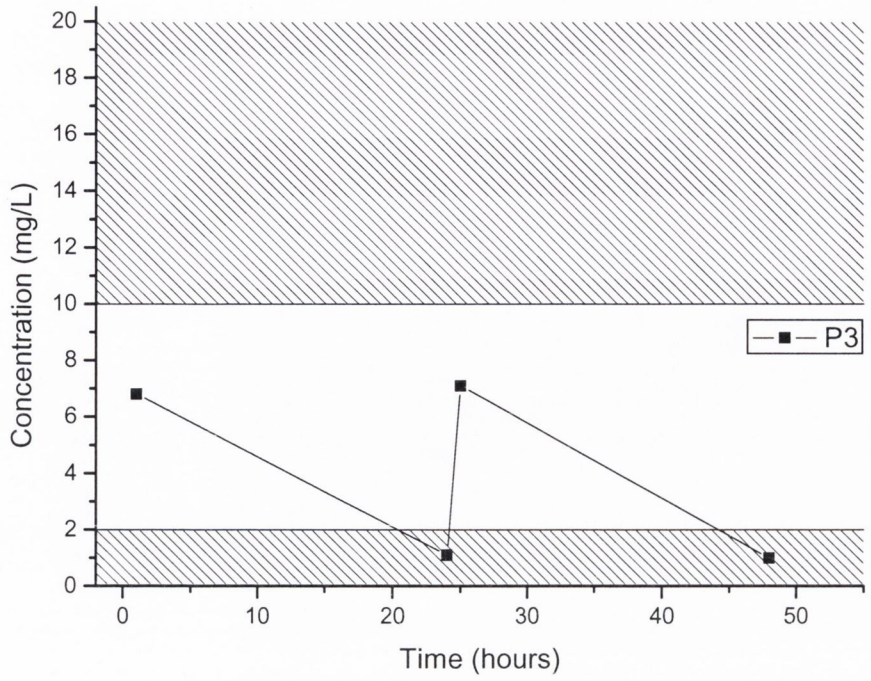


Figure 5.3.3: Gentamicin serum concentration-time data for Patient 3.

Similarly, in the treatment of E.coli and Pseudomonas infection in Patient 4, doses of 240mg and 260mg failed to achieve therapeutic concentrations, as defined by Hospital guidelines. In addition, on retrospective analysis it is clear that doses failed to attain individualised pharmacodynamic goals, based on microbiological sensitivity data. Achieving a (C_{pmax})/MIC of >10 within 48 hours of initiation of therapy for pneumonia caused by gram-negative organisms results in a 90% probability of therapeutic response by day 7 (204, 205).

Based on the Microscan system (Dade, West Sacramento, Calif.), the MIC at which 90% of the isolates are inhibited ($MIC_{90\%}$) for sterile body fluid (nonurine) isolates of Escherichia coli was 2μg/ml gentamicin. The MIC_{90} for Pseudomonas aeruginosa was 4μg/ml of gentamicin/ml. The C_{pmax}/MIC target must be chosen to achieve the maximum probability of response, considering the MIC_{90} s of the isolated gram-negative organisms and the upper limit of

aminoglycoside dose tolerability. For this patient with more resistant microorganisms (Aminoglycoside MICs >1μg/ml), targeting a C_{pmax}/MIC of 5 may be a reasonable approach, even though this C_{pmax}/MIC ration does not give a 90% probability of a therapeutic response (temperature and leucocyte resolution). The C_{pmax}/MIC ratio achieved in this patient was 3.4 and 1.7 for E.coli and P. aeruginosa isolates respectively.

5.4 Analysis of Therapeutic Drug Monitoring process based on Retrospective Analysis of Aminoglycoside Dosing and Serum Concentrations

5.4.1 Monitoring Aminoglycoside Serum Concentrations

Therapeutic Drug Monitoring is frequently used to make dosage adjustments for aminoglycosides. Unfortunately, serum samples obtained in clinical practice are often not optimally applied to improving patient care. Essential data such as the dose, time of serum sampling and time of the start and end of the infusion are not always accurately recorded, as previously reported in the literature and observed in the retrospective study, resulting in the exclusion of some data. However, this was easily remedied through educational intervention for medical and nursing staff, together with modification of the drug kardex and, for the purposes of this study, through the use of specifically designed data collection forms. Close attention was paid to the details of infusion start and end times and the time serum samples were drawn.

Prior to this study, clinicians monitored a peak or trough concentration and made empiric dosage adjustments. These empiric adjustments resulted in a trial and error period in which different dosage regimens were prescribed until optimal serum concentrations were achieved. However, this empiric, qualitative approach results in prolonged periods of suboptimal treatment,

incorrect dosage adjustments and, for some patients fails to achieve target serum concentrations at any stage during therapy. In addition to increasing the risk of therapy failure or toxicity, this approach is more likely to result in increased health-cost because of extended treatment duration and length of hospital stay. An objective of this study was to investigate an alternative approach for obtaining and interpreting serum concentrations in a controlled manner and using this data to estimate pharmacokinetic parameters in critically ill patients treated with CVVHDF. Initially, induction was provided to nursing staff on TDM practice and the records required for better control and achievement of target serum concentrations goals. At the same time, education of clinicians regarding the pharmacodynamic properties of the aminoglycosides was undertaken. Prior to this study, aminoglycoside monitoring had been undertaken with an emphasis on interpreting trough concentrations, in the same manner as for glycopeptides. However, aminoglycosides are quite different in terms of pharmacodynamic properties to vancomycin. As, aminoglycosides exhibit pronounced concentration-dependent killing, significant post antibiotic effect for gram negative organisms and adaptive resistance; the primary goals of dosing are to achieve a high C_{pmax} to MIC ratio and allow concentrations to fall below the MIC for a period of time before redosing. Despite these drug characteristics, trough concentrations had been used to guide aminoglycoside therapy and generally if trough concentrations were within the target range, dosage adjustment was not carried out, irrespective of peak concentrations. This resulted in the practice, observed in the retrospective study, whereby inadequate peak concentrations were ignored, as long as trough concentrations were below a target threshold. A number of steps were undertaken to address this practice. The ICU clinical pharmacist was consulted and the drug kardex

was modified to highlight the differences in the pharmacokinetic-pharmacodynamic basis for prescribing aminoglycosides and glycopeptides. In a designated section for prescribing these drugs, guidelines for both groups were separated, in order to emphasise the need for different approaches to their management, and target serum concentration ranges were highlighted on the kardex. Additionally, designated spaces for recording infusion times and sampling times were clearly delineated on the kardex. In conjunction with this, educational targeting of clinicians and senior nurse managers was carried out, to emphasise the need for controlled and accurate interpretation of aminoglycoside serum concentrations.

5.4.2 Using Aminoglycoside Serum Concentrations to Calculate Pharmacokinetic Parameters in Treated Patients

A method using serum concentration-time data from an individual patient to calculate an optimal dosage regimen has been developed (Sawchuk-Zaske method). This method uses serum-concentration data from an early dosage interval to determine each patient's pharmacokinetic parameters. Dosages can be individualised within the first 12 - 24 hours of therapy. The elimination rate constant, volume of distribution, half-life and clearance are calculated from a one-compartment fit of the measured serum-drug concentrations. After the desired peak and trough concentrations have been selected, the model parameter values are used to calculate the patient's dosage interval and dose to achieve these concentrations. This method allows target serum concentrations to be obtained early in therapy without the problems associated with the trial and error approach. Patients achieve therapeutic serum concentrations quickly thereby improving the likelihood of therapeutic success and reducing the risk of toxicity.

In the context of critical illness and CVVHDF therapy, with the likelihood of rapidly changing pharmacokinetic parameters and large interpatient variability, it is essential that aminoglycoside dosing is individualised and that serum concentrations are carefully interpretated and used to estimate individual patient parameters. This study applied the Sawchuk-Zaske method to an evaluation of aminoglycoside pharmacokinetics in critically ill patients treated with CVVHDF.

5.5 A Prospective Clinical and Pharmacokinetic Evaluation of Amikacin during CVVHDF therapy

5.5.1 Patients

Three men and two woman treated with amikacin during CVVHDF therapy, ages 57- 70 (mean +/- SD: 63.4 +/- 5.6 years) were enrolled in the study. The mean APACHE Π score was 26.6 +/- 7.8. The mean SOFA score was 5.4 +/- 1.1. One patient was treated with amikacin empirically for suspected sepsis. The reasons for starting CVVHDF therapy included ARF, Sepsis and Metabolic Acidosis. The mean duration of CVVHDF therapy was 11.0 +/- 2.7 days. Acinetobacter baumannii was isolated from two patients (patients 1 and 4), cultured from sputum and wound exudate respectively. A. baumannii is a multi-resistant aerobic gram-negative bacillus sensitive to relatively few antibiotics. For both patients; sensitivity data for A. baumannii reported sensitivity to amikacin. Pseudomonas aeruginosa was also isolated from sputum from patient 1 and was isolated from a blood culture in patient 2. P. aeruginosa is a Gram-negative, aerobic rod belonging to the bacterial family *Pseudomonadaceae* and is an opportunistic pathogen of humans. In both cases, isolates were sensitive to amikacin. Amikacin was prescribed for a further patient with systemic and respiratory infection due to klebsiella pneumoniae. All four patients, treated on the basis of sensitivity data, had concurrent gram-positive infection. Two patients were MRSA positive. Four of the five patients were diagnosed with sepis and two patients had concomitant liver and renal impairment. Demographic data and clinical characteristics are given in Table 5.5.1.

Table 5.5.1: Summary of Patients' Clinical and Demographic data

ID	Sex	Age	Diagnosis	Infective Diagnosis	APACHE Π Score[1]	SOFA Score[2]	SrCr[3] μmol	Cr Cl[4]	Duration CVVHDF (days)
P1	M	57	Cirrhosis of liver, ARF, sepsis, thrombocytopenia metabolic acidosis, anuric	Actinetobacter baumanni, Enterococcus Faecalis, Pseudomonas aeruginosa, Coag negative staph.	39	7	120	10	7
P2	F	68	Emergency Hartman's procedure for Colonic obstruction, post-op ARF, sepsis, Anuric	Enterococcus faecalis, Pseudomonas aeruginosa, MRSA	28	4	130	8	14
P3	M	59	Neutropenic sepsis, Septic shock, Tumor Lysis Syndrome with severe renal impairment, ALL, febrile, anuric, hypotensive	Empiric cover for suspected sepsis	24	5	180	5	10
P4	M	63	Cirrhosis of liver, emergency admission to ICU post leaking AAA repair	Acinetobacter Baumanni Coagulase negative staphylococci	18	6	194	5	13
P5	F	70	Pneumonia, SIRS, Sepsis, metabolic acidosis. COPD.	Klebsiella pneumoniae, Coagulase negative staphylococci	24	5	177	2	11

[1] Initial/ICU admission value [2] Initial/ICU admission value
[3] Serum creatinine value on day 1 of CVVHDF, prior to commencing CVVHDF therapy. Units = μmol/L.
[4] Creatinine clearance value on day 1 of CVVHDF, prior to commencing CVVHDF therapy. Units = ml/min; estimated using the method of Jelliffe and Jelliffe (42).

Estimates of CrCl were obtained using the method of Jeliffe and Jeliffe. All patients had severe renal impairment. Three patients were anuric throughout treatment (patients 1, 2, 3) and two patients were anuric on commencing CVVHDF but became oliguric during treatment (day 11 and day 10), at which time treatment with amikacin had stopped.

5.5.2 Pharmacokinetic Analysis and Clinical Discussion of 'peak' and trough amikacin serum concentrations:

Individual patient estimates of amikacin pharmacokinetic parameters during treatment with CVVHDF were obtained from amikacin serum concentration data. Pharmacokinetic parameters were first calculated using 'peak' and 'trough' amikacin serum concentrations, simulating routine TDM data, using the method of Sawchuk and Zaske (3). Estimates of amikacin pharmacokinetic parameters ($t_{1/2}$, Vd, Cl) obtained using this approach are presented for each patient in Table 5.5.2.

Table 5.5.2: Estimates of amikacin pharmacokinetic parameters derived from amikacin 'TDM' data.

Patient Profile	Dose (mg)	Dosage Interval (hours)	Cpmax (mg/L)	Cpmin (mg/L)	$t_{1/2}$ (hrs)	k (hr^{-1})	TBC (L/hr)	Vd (L)
P1A	900	24	31.3	3.0	7.07	0.098	3.026	30.88
P1B	900	24	33.8	4.0	7.79	0.089	2.642	29.69
P1C	1100	24	35.7	6.2	10.19	0.068	2.542	37.38
Mean					**8.35**	**0.085**	**2.737**	**32.65**
P2A	300	19	7.6	1.8	9.14	0.076	2.932	38.58
P2B	1500	24	50.2	2.8	5.78	0.120	3.659	30.49
P2C	1500	24	48.5	5.4	7.62	0.091	3.079	33.84
P2D	1500	29	49.4	5.0	8.45	0.082	2.712	33.08
P2E	1500	32	55.9	6.1	10.04	0.069	2.064	29.48
P2F	1500	29	53.8	7.0	9.90	0.070	2.168	30.97
Mean					**8.49**	**0.085**	**2.769**	**32.74**
CVVHDF Stopped P2G	1500	53.5	68.3	16.1	25.66	0.027	0.767	28.39
P3A	1500	24	44.9	2.8	5.99	0.116	4.062	34.45
P3B	1500	24	42.4	1.9	5.36	0.129	4.581	35.24
P3C	1500	24	46.5	2.1	5.37	0.129	4.238	32.60
Mean					**5.57**	**0.125**	**4.294**	**34.10**
P4A	600	12	16.2	4.0	5.46	0.127	5.321	44.37
P4B	600	12	23.4	5.0	5.63	0.123	3.732	31.07
Mean					**5.55**	**0.125**	**4.527**	**37.72**
P5A	1500	24	48.2	2.1	5.10	0.136	4.265	31.36
P5B	1500	25	52.4	2.4	5.41	0.128	3.709	28.98
P5C	1500	28	54.4	2.5	6.08	0.114	3.194	28.02
P5D	1500	28	55.8	2.5	6.03	0.115	3.144	27.34
Mean					**5.66**	**0.123**	**3.578**	**28.93**

One patient (P1) received an initial dose of 900mg once daily. The observed half-life was 7.07 hours, which corresponds to an elimination rate constant of $0.098hr^{-1}$. This dosing schedule did not achieve target C_{pmax} concentrations during CVVHDF therapy, with an ultrafiltration rate of 2.04 L/hr and a dialysate fluid rate of 1.02 L/hr. The high Vd observed in this patient contributed to the insufficiency of this dose. As this patient had severe sepsis, a high observed Vd for an aminoglycoside was not unexpected. Based on the estimates of pharmacokinetic parameters obtained from amikacin serum concentrations for this patient, it was estimated that a dose of 1500mg was necessary to achieve target C_{pmax} concentrations. The recommended course of action on the basis of PK data was to extend the dosage interval to 31 hours and to increase the dose to 1500mg. However, as there had been no previous experience of using such high doses of aminoglycosides in the Unit, a more conservative dose of 1100mg was prescribed. Figure 5.5.1 depicts the serum concentration data for this patient.

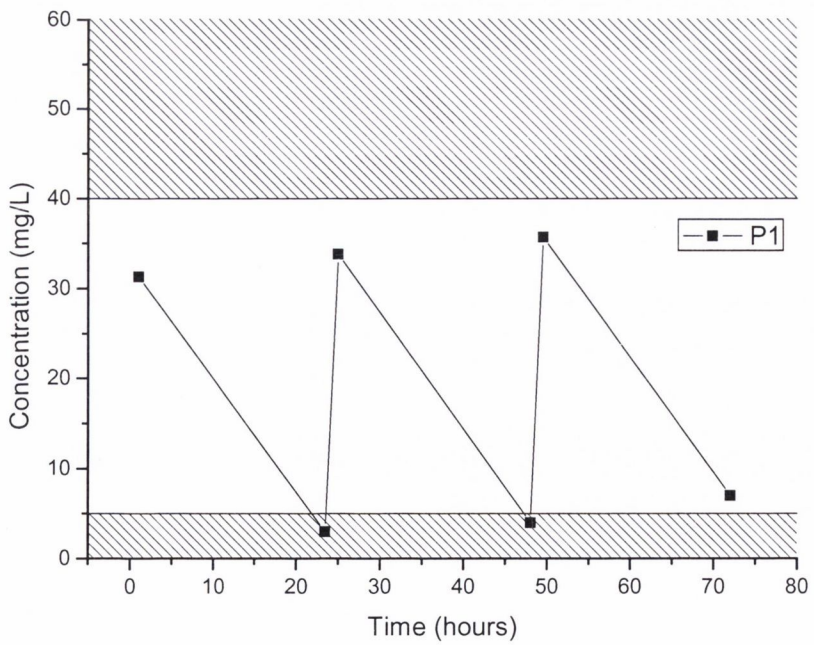


Figure 5.5.1: Amikacin serum concentration-time data for Patient 1.

In the case of the second patient (P2), the first dose administered, 300mg was prescribed by a doctor on-call, who was not aware that there had been a change towards using higher amikacin doses in patients treated with CVVHDF. Resulting amikacin serum concentrations were predictably inadequate. Subsequently, a 1500mg every 24 hours dosing schedule achieved effective amikacin C_{pmax} concentrations for this patient, but some extension of the dosage interval was required to prevent excessive trough concentrations (Figure 5.5.2). 'Once-daily' aminoglycoside dosing is more correctly described as extended-interval dosing and extension of the dosage far beyond 24 hours will be required in some patients with renal dysfunction. The importance of acknowledging this concept, rather than attempting to maintain a rigid 'once-daily' dosage interval, is illustrated in the cases of patients 1 and 2. In the treatment of the first patient, where strict 'once-daily' dosing was applied, lower doses at 24-hour intervals failed to achieve target peak concentrations, yet accumulation became evident. In contrast, in the case of patient 2, extension of the dosage interval beyond 24 hours, allowed target peak serum concentrations to be achieved, while limiting accumulation. Estimates of amikacin pharmacokinetic parameters (k, Vd, TBC) were similar for both patients ($p>0.05$) and the dosage recommendation for patient 2 was 1500mg every 32 hours. However, it is necessary to ensure that clinicians appreciate the impact of CVVHDF on amikacin clearance and thus the effect of stopping CVVHDF on amikacin serum concentrations, in a patient whose renal dysfunction has not resolved. In the case of patient 2, stopping CVVHDF therapy resulted in a three-fold increase in the amikacin half-life. Figure 5.5.2 shows amikacin serum concentrations over time for Patient 2. The arrow

indicates the point at which CVVHDF therapy was stopped and a subsequent increase in serum concentrations was observed.

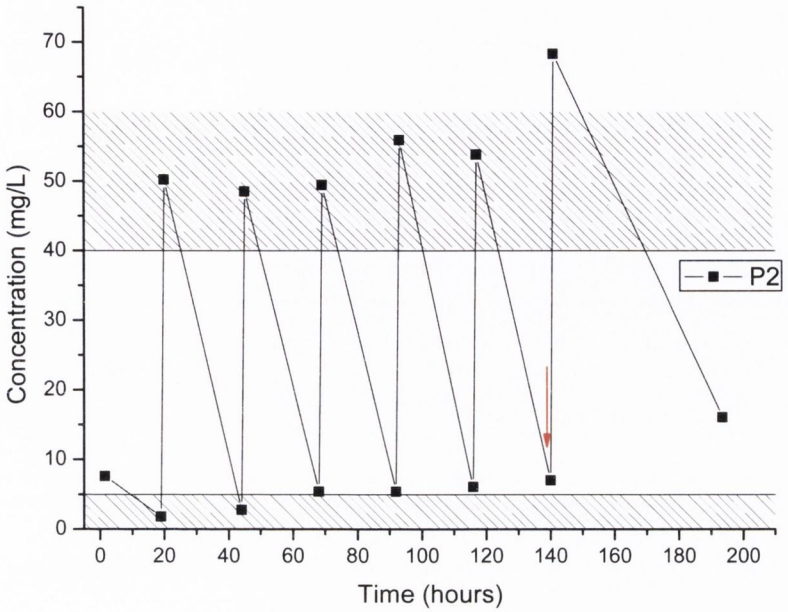


Figure 5.5.2: Amikacin serum concentration-time data for Patient 2.

For patient 3, a 1500mg dose achieved adequate C_{pmax} concentrations. C_{pmin} concentrations remained below the target threshold with a dosage interval of 24 hours. The mean half-life was 5.57 +/- 0.36 hours and the Vd was reasonably constant with a mean value of 34.1 +/- 1.4 L. The mean clearance estimate, 4.3 +/- 0.3 L/hr, was high and this value was close to the mean observed effluent flow rate during CVVHDF (4.1 L/hr). The serum concentration-time data for this patient is shown in Figure 5.5.3.

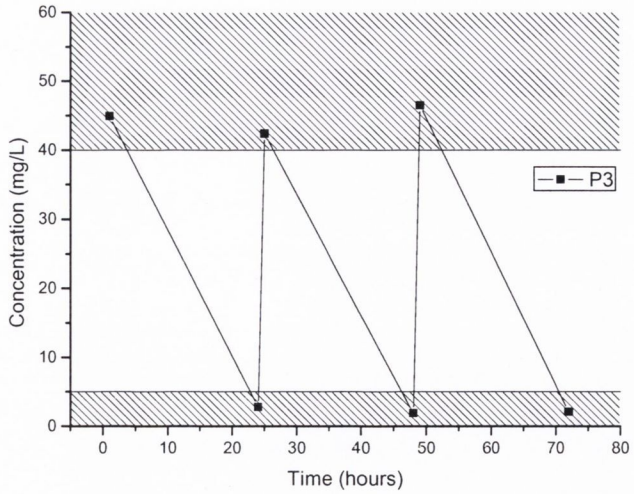


Figure 5.5.3: Amikacin serum concentration-time data for Patient 3.

Patient 4 was admitted to ICU on a Thursday afternoon and CVVHDF therapy was commenced as part of the management of sepsis and ARF. On the Friday morning microbiology ward round, a decision was made to start amikacin on Saturday if pyrexia persisted and pending sensitivity data reports. This decision was recorded in the medical notes but no guidance on dosing was included. Actinetobacter baumanni was subsequently isolated from sputum samples and amikacin therapy was initiated on Saturday. However, the dose prescribed did not comply with the recently introduced guidelines for aminoglycoside dosing during CVVHDF. Instead of administering a high dose at extended interval, 600mg amikacin was administered twice daily. The C_{pmax} concentration achieved by the 600mg dose was 16.2 mg/L and the C_{pmin} concentration was 4mg/L. There was a significant change in the observed Vd between the two dosage intervals, 44.4 L and 31.1 L respectively, and this was reflected in a decrease in the estimated clearance from 5.32 to 3.73 L/hr. The half-life remained quite constant, at approximately 5.5 hours.

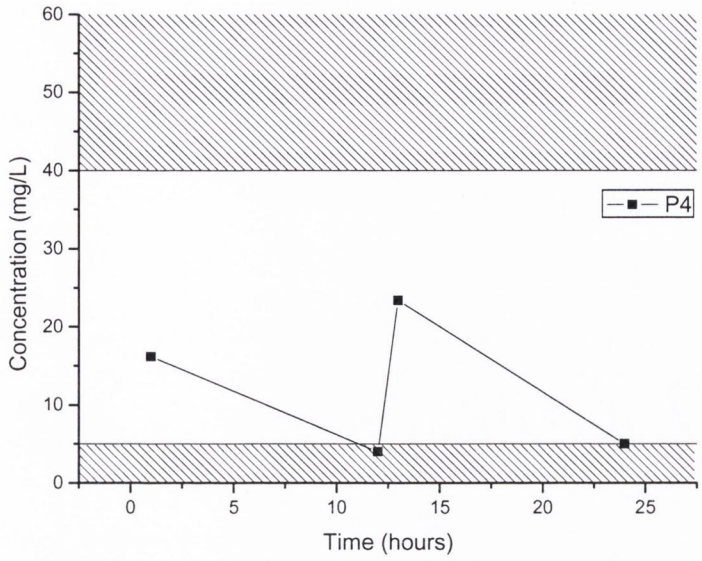


Figure 5.5.4: Amikacin serum concentration data for Patient 4.

(The shaded regions represent target Cpmax and Cpmin concentration ranges for extended interval dosing – this was a twice daily dosing schedule).

For patient 5, a dosing schedule of 1500mg once daily achieved effective C_{pmax} concentrations, based on a target C_{pmax}/MIC ratio of 10. The MIC for the sensitive micro-organism was 5ug/ml amikacin. For profiles C and D, the dosage interval was extended somewhat to avoid excessively high C_{pmin} concentrations, as the predicted C_{pmin} concentration with a dosage interval of 24 hours had been higher than the observed value (3.4mg/L). Serum concentration-time data for this patient is depicted in Figure 5.5.5.

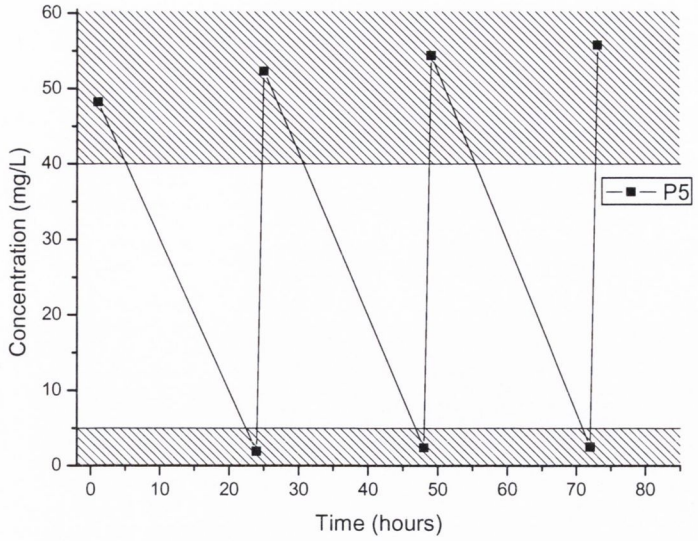


Figure 5.5.5: Amikacin serum concentration time data for Patient 5.

Among this patient sample, a trend of a decreasing Vd for amikacin during CVVHDF therapy appeared to emerge. This may relate to physiological changes resulting from treatment with CVVHDF.

5.5.3 Pharmacokinetic analysis of multiple amikacin serum concentrations in a dosage interval

A similar approach to that used in the analysis of vancomycin serum concentrations in the previous chapter was applied to amikacin serum concentration data, where multiple blood samples had been taken in a single dosage interval. This multiple amikacin serum concentrations in a dosage interval-time data is presented graphically in Figure 5.5.6.

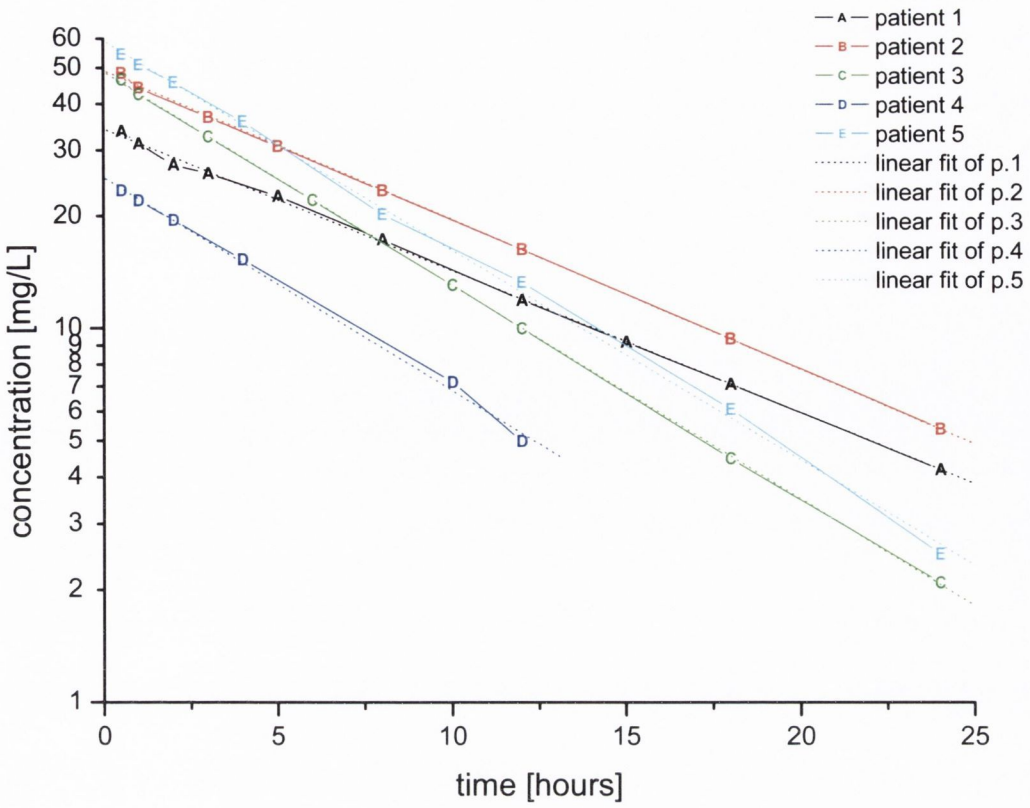


Figure 5.5.6: Multiple amikacin serum concentrations in a dosage interval over time (linear fit) for all patients treated concurrently with amikacin and CVVHDF.

Best-fit parameters for each model are compared in Table 5.5.3 and individual patient parameters are given in Tables 5.5.4 and 5.5.5.

Table 5.5.3: Best-fit parameters for monoexponential and biexponential models.

Model	Least Sum of Squares	MSC	r^2	Correlation
Biexponential	0.00528 +/- 0.00048	2.96 +/- 0.13	0.992 +/- 0.02	0.972 +/- 0.008
Monexponential	0.00538 +/- 0.0097	2.89 +/- 0.19	0.991 +/- 0.00	0.972 +/- 0.011

Estimates of pharmacokinetic parameters, k, Cl and Vd, were initially obtained for each patient on the basis of a one-compartment model. These individual patient parameters estimates for amikacin during CVVHDF therapy are tabulated below:

Table 5.5.4: Individual patient estimates of amikacin pharmacokinetic parameters during treatment with CVVHDF, obtained from multiple amikacin serum concentrations in a dosage interval fitted to a one-compartment model

ID	k (hr^{-1})	Vd (L)	TBC (L/hr)	Least sum of squares	MSC	r^2	Corr.
1	0.067	39.12	2.621	0.00448	3.14	0.9929	0.9798
2	0.076	38.64	2.937	0.00699	2.64	0.9874	0.9532
3	0.110	35.01	3.851	0.00519	2.74	0.9906	0.9785
4	0.125	32.14	4.017	0.00542	2.87	0.9912	0.9698
5	0.127	28.48	3.617	0.00481	3.06	0.9909	0.9771
Mean +/- s.d.	**0.101 +/- 0.028**	**34.68 +/- 4.48**	**3.409 +/- 0.602**	**0.00538 +/- 0.0097**	**2.89 +/- 0.19**	**0.991 +/- 0.002**	**0.972 +/- 0.011**

The same amikacin serum concentration time data, obtained from multiple blood samples in a dosage interval, was then fitted to a two-compartment model and associated estimates of pharmacokinetic parameters, k_{el}, $t_{1/2\alpha}$, $t_{1/2\beta}$, Vd_{ext}, were calculated. Estimates of individual patient parameters are given below:

Table 5.5.5: Individual patient estimates of amikacin pharmacokinetic parameters during CVVHDF therapy

ID	k_{el} (hr^{-1})	V_1 (L)	TBC (L/hr)	$T_{1/2\alpha}$ (hrs)	$T_{1/2\beta}$ (hrs)	$T_{1/2el}$ (hrs)	Least sum of squares	MSC	r^2	Corr.
1	0.068	36.667	2.493	0.12	10.34	10.19	0.00492	3.01	0.9936	0.9736
2	0.079	35.886	2.835	0.40	8.88	8.77	0.00601	2.99	0.9895	0.9601
3	0.121	34.510	4.538	0.17	5.81	5.73	0.00549	2.97	0.9921	0.9754
4	0.125	30.005	3.751	0.09	5.63	5.54	0.00486	3.08	0.9946	0.9710
5	0.127	28.281	3.952	0.29	5.41	5.46	0.00512	3.02	0.9917	0.9812
x	**0.104**	**34.237**	**3.514**	**0.214**	**7.214**	**7.138**	**0.00528**	**3.01**	**0.992**	**0.972**
s. d.	**0.028**	**3.427**	**0.837**	**0.129**	**2.252**	**2.198**	**0.00048**	**0.04**	**0.02**	**0.008**

Paired student t-tests were carried out on mean estimates of pharmacokinetic parameters derived from a one- and two-compartment model (Vd versus V_1, k versus k_{el} and TBC_{mono} versus TBC_{biexp}). These estimates of pharmacokinetic parameters, obtained by fitting multiple amikacin serum concentrations to a monoexponential or biexponential model, were also compared with pharmacokinetic parameters estimates (Cl, Vd, k) obtained from 'TDM-type' data, where only 'peak' and trough concentrations from the same patients were used. Estimates of amikacin pharmacokinetic parameters, derived from a monoexponential model versus a biexponential model, did not differ at a significance level of 0.05 (Table 5.5.6).

Table 5.5.6: Comparison of estimates of amikacin pharmacokinetic parameters derived by fitting multiple serum amikacin concentrations in a dosage interval to both one and two compartment models

Parameter	**k**	**k_{el}**	**p<0.05**
Mean (sd)	0.101 +/- 0.028	0.104 +/- 0.028	NSS
Parameter	**Vd**	**V_1**	
Mean (sd)	34.68 +/- 4.48	34.24 +/- 3.43	NSS
Parameter	**Cl_{mono}**	**Cl_{biexp}**	
Mean (sd)	3.41 +/- 0.60	3.51 +/- 0.84	NSS

Estimates of pharmacokinetic parameters obtained by applying the Sawchuk and Zaske method to 'peak' and trough amikacin concentrations are compared to estimated obtaining by fitting multiple serum amikacin concentrations (MSC) to a one-compartment model in Table 5.5.7:

Table 5.5.7: Comparison of estimates of amikacin pharmacokinetic parameters obtained from multiple serum amikacin concentrations fitted to a one-compartment model versus those estimated from TDM data.

Parameter	**k (MSC)**	**k (TDM)**	**p<0.05**
Mean (sd)	0.101 +/- 0.028	0.104 +/- 0.027	NSS
Parameter	**Vd (MSC)**	**Vd(TDM)**	
Mean (sd)	34.68 +/- 4.48	33.23 +/- 4.45	NSS
Parameter	**TBC (MSC)**	**TBC(TDM)**	
Mean (sd)	3.41 +/- 0.60	3.46 +/- 0.61	NSS

5.5.4 Amikacin Clearance due to CVVHDF

Details of amikacin and creatinine clearance due to CVVHDF and details of CVVHDF conditions are given in Table 5.5.8. The mean clearance of amikacin by CVVHDF was 2.86 +/- 0.41 L/hr, which was 91% of the total body clearance. The sieving coefficient for amikacin was 0.83 +/- 0.05, which was consistent with that previously reported in the literature, although different filters and CRRT conditions were in use (224, 226). The observed sieving coefficient was slightly lower than the unbound fraction of amikacin. Factors that influence sieving coefficients include alterations in serum concentration of protein, albumin or bilirubin, administration of heparin, TPN and fat emulsion, changes in blood pH or in degree of uraemia. The amikacin clearance due to CVVHDF estimated using the sieving coefficient; 2.93 L/hr, was similar to the actual measured clearance (2.86 L/hr). Creatinine clearance (2.7 +/- 0.4 L/hr) by the filter was slightly less than amikacin clearance. The sieving coefficient for creatinine was 0.80 +/- 0.1. This value was very close to the sieving coefficient for amikacin, but was slightly lower and more variable.

Table 5.5.3: Clearance of amikacin and creatinine by CVVHDF and summary of CVVHDF system conditions

Patient Profile	Cl_{CVVHDF} (L/hr)	F_{CVVHDF}	Clcreat (L/hr)	Actual Effluent flow rate (L/hr)	Number of filters ^	Age of Filter* (hrs)
P1C	2.53	0.97	2.19	3.16	1	16
P2D	2.55	0.98	2.70	2.91	1	27
P3A	3.40	0.84	3.20	4.10	1	1
P5B	2.97	0.80	2.86	3.95	1	26

*At start of dosage interval
^ During dosage interval

5.6 A Prospective Clinical and Pharmacokinetic Evaluation of Gentamicin during CVVHDF therapy

5.6.1 Patients

Seven patients were enrolled in this prospective analysis. Four men and three women were concurrently treated with gentamicin and CVVHDF therapy, as clinically indicated. Demographic data and clinical characteristics are given in Table 6.1.The mean age was 61.3 +/- 15.3 years. The mean APACHE score was 29.1 +/- 6.8 and the mean SOFA score was 6.86 +/- 1.77. The mean duration of CVVHDF therapy was 10.1 days. Five patients were treated for documented Gram-negative infection and two patients were treated empirically for suspected sepsis. The most commonly isolated microorganisms sensitive to Gentamicin were Escherichia coli and Pseudomonas aeruginosa.

The mean effluent rate achieved was 2.7 +/- 0.4 L/hr. The most commonly prescribed ultrafiltration rate was 2.0 L/hr and the dialysate rate was 1.0 L/hr. The mean duration of use of a filter was 51.8 hours. During the treatment of patient 2, filter clots occurred while obtaining pharmacokinetic profiles F and G and in both cases there were significant interruptions to CVVHDF therapy of 6.7 and 7.2 hours respectively.

Table 5.6.1: Patient Demographics and Clinical Characteristics

ID	Sex	Age	Diagnosis	Infective Diagnosis	APACHE II Score[1]	SOFA Score[2]	Sr Cr[3]	Cr Cl[4]	CVVHDF Duration (days)
P1	M	34	Multiple trauma, sepsis, hepatic impairment.	Escherichia coli	29	8	88	9	9
P2	F	68	Emergency Hartman's procedure for Colonic obstruction, post-op acute renal failure and sepsis, oedema, anuric	Enterococcus faecalis, Pseudomonas aeruginosa, MRSA	27	6	134	5	14
P3	M	50	Listeria monocytogenes meningitis, CLL, Sepsis	Klebsiella pneumoniae, MRSA	31	5	86	6	6
P4	M	57	Alcoholic liver disease, thrombocytopenia, sepsis, metabolic acidosis, ARF, anuric.	Actinetobacter baumanni, Enterococcus Faecalis, Pseudomonas aeruginosa, staphylococci	30	9	120	3	7
P5	F	69	Diabetic Nephropathy, ARF, sepsis, septic shock, jaundice, respiratory failure,anuric	Enterobacter cloacae	28	9	117	3	9
P6	M	74	ARF, sepsis.	E. coli, Citrobacter freundii, Klebsiella pneumonia, Staph. aureus, Clostridium perfringens, MRSA	24	5	72	8	15
P7	F	77	Pneumoniae, ARF, sepsis	Klebsiella, E.coli	26	6	108	4	11

[1] Admission value/Initial ICU value

[2] Admission value/Initial ICU value

[3] Estimated on day 1 of CVVHDF, prior to commencing therapy. Units = μmol/L

[4] Estimated on day 1 of CVVHDF, prior to commencing therapy. Units = ml/min, estimated using Jelliffe method (42).

5.6.2 Gentamicin Serum Concentration – Time Data

1. TDM data ('peak' and trough concentrations)

Individual patient pharmacokinetic parameters for amikacin estimated using 'peak' and trough concentrations (TDM-type data) are given in Table 5.6.2.

Table 5.6.2: Pharmacokinetic parameters estimated for individual patients from simulated 'TDM' data

Patient Profile	Dose (mg)	T (hrs)	Cpmax (mg/L)	Cpmin (mg/L)	Half-life (hrs)	k (hr^{-1})	Cl (L/hr)	Vd (L)
P1A	240	24	6.8	0.9	7.89	0.088	3.480	39.54
P1B	280	24	9.3	0.9	6.79	0.102	3.298	32.33
P1C	280	24	8.2	1.0	7.90	0.088	3.328	37.82
P1D	320	24	10.1	1.2	7.48	0.093	3.281	35.28
P1E	360	24	10.8	1.3	7.53	0.092	3.386	36.81
P1F	360	24	11.2	1.3	7.40	0.093	3.319	35.69
Mean					**7.49**	**0.093**	**3.349**	**36.24**
P2A	340	24	9.7	1.5	8.54	0.081	3.357	41.44
P2B	340	28	10.8	Unde*	NA	NA	NA	NA
P2C	360	24	11.2	1.5	7.93	0.083	3.034	36.55
P2D	360	24	11.4	1.5	8.15	0.085	3.041	35.78
P2E	320	24	10.4	1.1	7.10	0.098	3.272	33.39
P2F	320	24	12*	2.5*	10.16	0.068	2.232	32.83
P2G	320	24	18.5*	3.8*	10.07	0.069	1.484	21.51
Mean					**8.66**	**0.081**	**2.737**	**33.58**
P3A	320	24	11.7	1.0	6.76	0.102	2.960	29.02
P4A	360	24	13.1	1.2	6.96	0.099	2.936	29.66
P4B	400	24	14.9	1.4	7.03	0.098	2.819	28.77
P4C	400	26	15.3	1.6	7.67	0.090	2.556	28.40
Mean					**7.22**	**0.096**	**2.770**	**28.94**
P5A	280	24	9.2	1.1	7.50	0.092	3.089	33.58
P5B	300	25	10.1	0.9	7.17	0.097	3.104	32.00
P5C	320	24	10.8	1.1	7.28	0.095	3.012	31.71
P5D	360	27	11.3	1.0	7.72	0.089	3.062	34.41
Mean					**7.42**	**0.093**	**3.067**	**32.93**
P6A	280	24	13.7	1.9	**8.07**	**0.085**	**1.984**	**23.34**
P7A	320	24	11.0	1.5	8.01	0.086	2.817	32.75
P7B	360	24	15.7	1.9	7.55	0.091	2.331	25.62
P7C	360	24	15.9	1.2	6.17	0.112	2.656	23.71
Mean					**7.24**	**0.096**	**2.601**	**27.36**

*There were significant interruptions to CVVHDF therapy during these two dosage intervals (6.7 and 7.2 hours)

Dosage adjustment on the basis of parameter estimates, obtained during the first and second dosage intervals, was required to achieve therapeutic serum concentrations for Patient 1. On the basis of a one-compartment model, it was predicted following the second dosage interval that a dose of 360mg every 24 hours should achieve a C_{pmax} concentration > 10mg/L and a Cpmin concentrations < 2mg/L. This dose was administered and target serum concentrations were observed. In the treatment of Patient 2, the dosage interval was inadvertently extended to 29 hours following administration of the second dose. The 'trough' sample was assayed and any gentamicin present was undetectable but there may have been a 'drug-free period'. Gentamicin half-life estimates were consistent (approximately 7-8 hours) for this patient while CVVHDF conditions remained constant (profiles A, C, D, E), but significant interruptions to CVVHDF therapy resulted in an extended half-life and some degree of accumulation; with trough concentrations exceeding 2mg/L (profiles F, G). A gradual decrease in gentamicin Vd occurred during CVVHDF therapy. CVVHDF therapy was prescribed to treat fluid overload and oedema, resulting from ARF in this patient. This observed intrapatient variability during therapy is easily explained, in that a patient who is initially fluid overloaded at the start of therapy will be expected to experience a decrease in Vd with subsequent treatment, due to the distribution characteristics of gentamicin. These changes may have a significant effect on serum concentrations and dosage requirements. Additionally, changes in the patient's cardiovascular haemodynamics and the extracellular fluid compartment may change the drug's clearance and distribution volume. For example, in a patient with oedema and fluid overload, the cardiac output, renal blood flow, glomerular filtration and drug clearance may increase, provided the CVS can tolerate the

fluid load. Thus, the observed changes in gentamicin serum concentrations during profiles F and G, relative to those in earlier dosage intervals, may be a product of changing CVVHDF conditions and the patient's altered physiological status.

In the case of patient 3, this patient had been receiving gentamicin 160mg every 24 hours for three days, prior to the commencement of CVVHDF therapy. On starting CVVHDF therapy, a recommendation to increase the dose to 320mg every 24 hours initially, with extension of the dosage interval based on levels, was suggested. This dose was administered and measured gentamicin serum concentrations were within the target range. A decision was made on day 2 of CVVHDF therapy to discontinue gentamicin therapy and start treatment with ciprofloxacin.

For patient 4, MIC data for isolated pseudomonas aeruginosa was available and thus an individualised PK-PD goal could be targeted. The MIC_{90} for Pseudomonas aeruginosa was 3μg/ml of gentamicin. The optimum C_{pmax}/MIC ratio would require a target C_{pmax} of 30mg/L. However, considering the upper limit of gentamicin dose tolerability, a target C_{pmax}/MIC ratio of 5 was considered reasonable and a target C_{pmax} concentration of 15mg/L was used for the purpose of dosing schedule design. On the basis of an estimated half-life of 7 hours and a Vd of 30L (obtained from gentamicin serum concentrations during the first dosage interval) and assuming a one-compartment model, it was suggested that a dose of 400mg every 24 hours should achieve target serum concentrations. The likely need for subsequent extension of the dosage interval, in response to a changing Vd and/or some degree of accumulation, which is inevitable with aminoglycosides due to tubular reasborption, was emphasised.

For patient 5, there was little variability in gentamicin pharmacokinetic parameters throughout CVVHDF therapy. Adjustment of each dosing schedule was made on the basis of the pharmacokinetic parameters estimated from serum concentration data during the previous dosage interval and a target Cpmax concentration of 11mg/L.

In the case of patient 7, there was an increase in k and a decrease in Vd during CVVHDF therapy, while gentamicin TBC remained constant. The initial dose prescribed was adjusted on the basis of estimated PK parameters to achieve a target Cpmax concentration of 15mg/L.

5.6.3 Gentamicin Pharmacokinetics during CVVHDF assessed using 'TDM' data.

The mean C_{pmax} concentration was 11.76 +/- 3.12 mg/L and the mean Cpmin concentration was 1.44 +/- 0.67 mg/L. Gentamicin half-life ($t_{1/2}$) ranged from 6.2 – 10.2 hours during CVVHDF therapy. The mean $t_{1/2}$ value was 7.07 +/- 1.76 hours and the mean elimination rate constant was 0.087 +/- 0.020 hr^{-1}. Gentamicin half-life is approximately 3 hours in patients with normal renal function and so the observed half-life during CVVHDF therapy is approximately twice the 'normal' half-life. This is similar to our observations of vancomycin half-lives during CVVHDF therapy. The mean gentamicin half-life during CVVHDF therapy was far shorter than that previously reported for gentamicin during treatment with a less efficient form of RRT. A report of gentamicin elimination in a single patient undergoing CAVU observed a half-life of 65.4 hours.

The Vd ranged from 21.5L to 41.4L (Mean = 30.3 +/- 7.6 L). Observed inter- and intra- patient Vd variability is consistent with previous literature reports

and in general a trend of a fall in Vd during treatment with CVVHDF was detected. The mean Clearance was 2.7 +/- 0.7 L/hr.

5.6.4 Multiple Gentamicin Serum Concentrations in a Dosage Interval

In the previous section, the use of gentamicin 'peak' and trough concentrations in estimating individual patient pharmacokinetic parameters and optimising dosing schedules during CVVHDF therapy was discussed. In this section, pharmacokinetic parameters calculated by fitting multiple serum gentamicin concentrations in a dosage interval to one and two- compartmental models will be compared for the same patient sample. Figure 5.6.1 presents the best linear fits and measured gentamcin concentrations for the seven patients analysed.

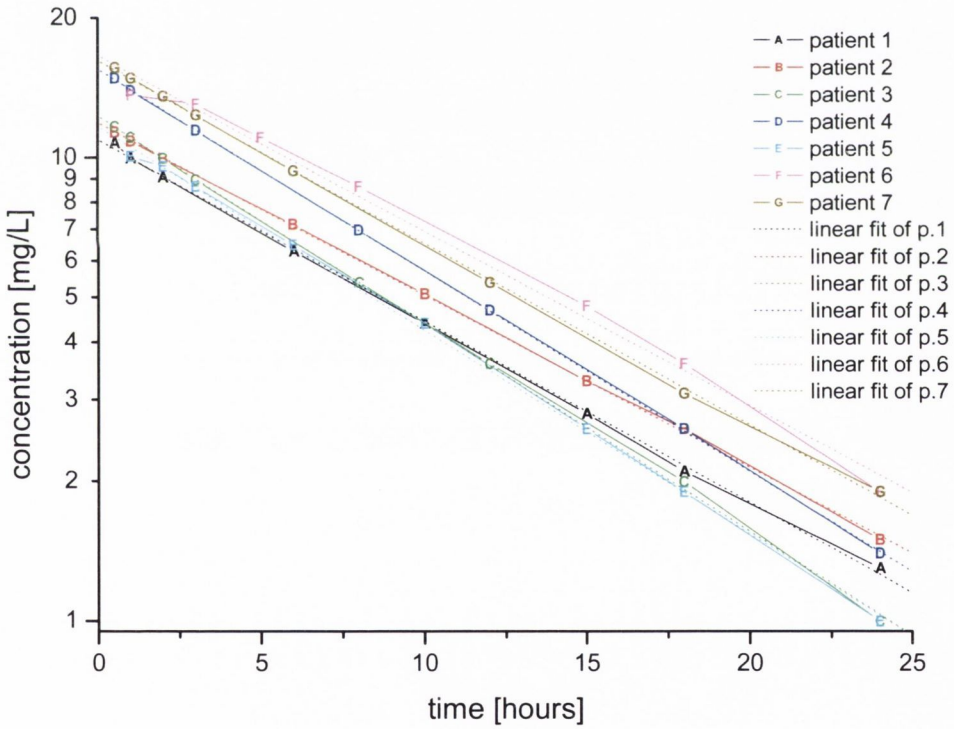


Figure 5.6.1: Multiple gentamicin serum concentrations in a dosage interval for seven patients treated concurrently with gentamicin and CVVHDF therapy.

In this section, gentamicin pharmacokinetic parameters calculated by fitting multiple gentamicin serum concentrations in a single dosage interval to a monoexponential or biexponential model will be compared to those obtained using 'peak' and trough concentrations alone. Estimates of pharmacokinetic parameters, k, TBC and Vd, were obtained for each patient first on the basis of a one-compartment model. These individual patient parameter estimates for gentamicin during CVVHDF therapy are tabulated in Table 5.6.4:

Table 5.6.3: Estimates of individual patient estimates of gentamicin pharmacokinetic parameters derived from multiple gentamicin serum concentrations in a dosage interval fitted to a one-compartment model.

Patient ID	k (hr^{-1})	Vd (L)	TBC_{mono} (L/hr)	Least sum of squares	MSC	R^2	Corr.
1	0.087	38.10	3.315	0.00412	3.20	0.9927	0.9749
2	0.084	35.98	3.022	0.00594	2.94	0.9864	0.9682
3	0.099	28.96	2.925	0.00509	3.05	0.9906	0.9725
4	0.098	27.88	2.732	0.00482	3.12	0.9912	0.9708
5	0.096	31.17	2.992	0.00514	2.97	0.9887	0.9671
6	0.085	28.73	2.442	0.00498	3.04	0.9896	0.9699
7	0.090	27.77	2.527	0.0050	3.03	0.9834	0.9649
Mean +/- sd	0.091 +/- 0.006	31.227 +/- 4.171	2.851 +/- 0.304	0.005 +/- 0.005	3.05 +/- 0.09	0.989 +/- 0.003	0.970 +/- 0.003

The same gentamicin serum concentration time data, obtained from multiple blood samples in a dosage interval, was then fitted to a two-compartment model and associated estimates of pharmacokinetic parameters, k_{el}, $t_{1/2\alpha}$, $t_{1/2\beta}$, Vd_{ext}, were calculated.

Table 5.6.5: Gentamicin pharmacokinetic parameters during CVVHDF therapy calculated using multiple serum gentamicin concentrations.

ID	k_{el} (hr^{-1})	V_1 (L)	TBC_{bi} (L/hr)	$t_{1/2\alpha}$ (hrs)	$t_{1/2\beta}$ (hrs)	$t_{1/2el}$ (hrs)	Least sum of squares	MSC	r^2	Corr.
1	0.087	37.64	3.362	0.11	7.89	7.96	0.00408	3.22	0.9919	0.979
2	0.083	34.22	2.989	0.19	8.10	8.34	0.00496	3.17	0.9894	0.968
3	0.101	27.14	2.954	0.22	6.79	7.01	0.00487	3.10	0.9918	0.975
4	0.098	26.96	2.936	0.24	7.05	7.07	0.00497	2.98	0.9922	0.968
5	0.095	30.86	3.123	0.31	7.14	7.29	0.00542	3.11	0.9887	0.964
6	0.085	27.34	2.491	0.27	8.06	8.15	0.0051	2.89	0.9881	0.968
7	0.091	26.11	2.529	0.13	7.52	7.70	0.00427	3.24	0.9934	0.979
Mean	**0.092**	**30.04**	**2.912**	**0.21**	**7.51**	**7.65**	0.0048	3.10	0.9908	0.971
s.d	**0.007**	**4.41**	**0.311**	**0.07**	**0.53**	**0.53**	0.0005	0.13	0.0020	0.006

Estimates of gentamicin pharmacokinetic parameters derived using both models were compared as for amikacin. The same statistical tests (student t-tests) were carried out on mean estimates of pharmacokinetic parameters (Vd versus Vdext, kel versus k and Cl) derived from a one- and two-compartment model. These estimates of pharmacokinetic parameters were also compared with pharmacokinetic parameters estimates (Cl, Vd, k) obtained from gentamicin 'TDM-type' data. Estimates of gentamicin pharmacokinetic parameters, derived from a monoexponential model versus a biexponential model, did not differ at a significance level of 0.05 (Table 5.6.5).

Table 5.6.6: Comparsion of estimates of gentamicin pharmacokinetic parameters derived by fitting multiple serum gentamicin concentrations in a dosage interval to both one and two compartment models

Patient[1]	k_{el} (hr^{-1})	K (hr^{-1})	V_1 (L)	Vd (L)	TBC_{biexp} (L/hr)	TBC_{mono} (L/hr)
1	0.087	0.087	37.64	38.10	3.275	3.315
2	0.084	0.083	34.22	35.98	3.2874	3.022
3	0.101	0.099	27.14	28.96	2.741	2.925
4	0.098	0.098	26.96	27.88	2.642	2.732
5	0.096	0.095	30.86	31.17	2.963	2.992
6	0.085	0.085	27.34	28.73	2.324	2.442
7	0.091	0.090	26.11	27.77	2.376	2.527
Mean	**0.092**	**0.091**	**30.04**	**31.23**	**2.742**	**2.851**
s.d.	**+/- 0.007**	**+/- 0.006**	**+/- 4.41**	**+/- 4.18**	**+/- 0.393**	**+/- 0.304**

Data in rows 2-8 represents the best estimate of each parameter for each individual patient

Row 9 contains the sample mean parameter value

Estimates of pharmacokinetic parameters obtained by applying the Sawchuk and Zaske method to 'peak' and trough gentamicin concentrations are compared to those estimated by fitting multiple serum gentamicin concentrations to a one-compartment model in Table 5.6.7.

Table 5.6.7: Comparison of gentamicin pharmacokinetic parameters obtained multiple serum amikacin concentrations fitted to a one-compartment model and those estimated from TDM data.

Patient[1]	k_{SZM} (hr^{-1})	K (hr^{-1})	Vd_{SZM} (L)	Vd (L)	TBC_{SZM} (L/hr)	TBC (L/hr)
1	0.093	0.087	36.24	38.10	3.349	3.315
2	0.081	0.083	33.58	35.98	2.737	3.022
3	0.102	0.099	29.02	28.96	2.960	2.925
4	0.096	0.098	28.94	27.88	2.770	2.732
5	0.093	0.095	32.93	31.17	3.067	2.992
6	0.085	0.085	23.34	28.73	1.984	2.442
7	0.096	0.090	27.36	27.77	2.601	2.527
Mean +/- s.d.	**0.092 +/- 0.007**	**0.091 +/- 0.006**	**30.20 +/- 4.35**	**31.23 +/- 4.17**	**2.781 +/- 0.429**	**2.851 +/-** 0.304

5.6.5 Effluent fluid data: Gentamicin and Creatinine clearance due to CVVHDF

Gentamicin and creatinine clearances due to CVVHDF are presented in Table 5.6.8. A sieving coefficient was obtained by comparing Gentamicin serum concentrations with effluent fluid concentrations for a complete dosage interval (and two dosage intervals in the case of Patient 7). The sieving coefficient for gentamicin was 0.85 +/- 0.05. The mean clearance of Gentamicin due to CVVHDF was 2.3 +/- 0.3 L/hr. This is 82% of the total body clearance of gentamicin.

Table 5.6.8: CVVHDF Clearance of Gentamicin and Creatinine.

Patient Profile	Cl_{CVVHDF} (L/hr)	Cl_{CREAT} (L/hr)	F_{CVVHDF}	Measured effluent fluid rate (L/hr)	Total Body Clearance (L/hr)
1C	2.90	2.60	0.87	3.25	3.33
2D	2.41	2.22	0.79	2.81	3.04
3A	2.63	2.35	0.88	3.01	2.96
4B	2.25	2.22	0.80	2.78	2.82
5A	2.10	1.91	0.68	2.36	3.09
5B	2.18	1.94	0.70	2.43	3.10
6A	1.81	1.64	0.91	2.05	1.98
7B	2.30	2.60	0.99	3.02	2.33
Mean +/-	2.32 +/-	2.22 +/-	0.83 +/-	2.71 +/- 0.40	2.83 +/-
SD	0.33	0.35	0.11		0.45

Figure 5.6.1 illustrates mean gentamicin and creatinine clearance over time. Creatinine clearance was 2.22 +/- 0.35 L/hr and so was slightly less and more variable than gentamicin clearance.

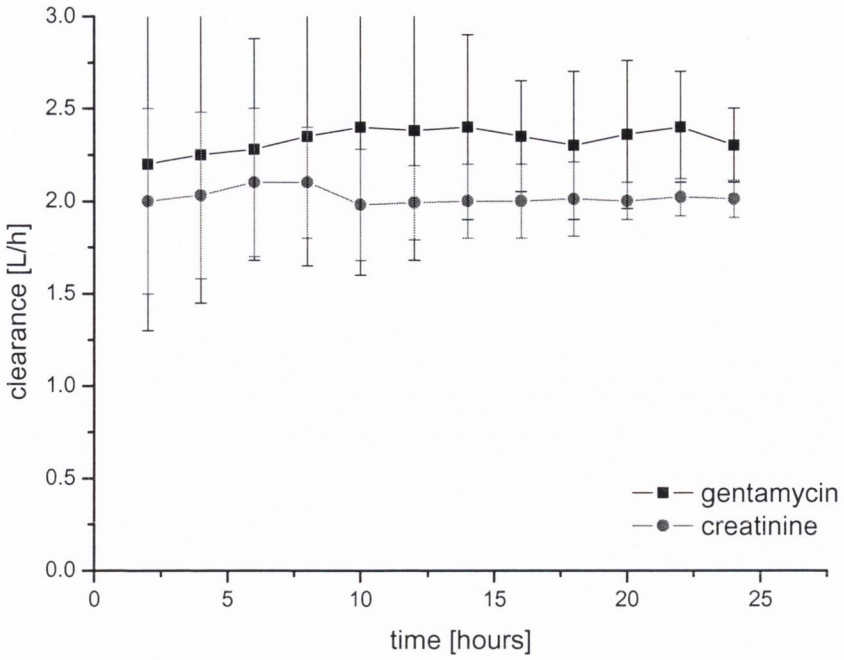


Figure 5.6.3: Comparison of mean Gentamicin and Creatinine Clearances by CVVHDF over time.

Gentamicin and creatinine clearances for each 2-hour period were examined over a dosage interval for each patient. In the case of Patients 2 (C) and 4 (A), a gradual increase in the gentamicin effluent fluid concentration/serum concentration ratio was observed (Figures 5.6.3 and 5.6.4), but the total clearance over the dosage interval was similar to that observed for other dosage intervals, where clearance remained constant. Thus, although there appears to be some initial adsorption of gentamicin to the filter, this appears to be followed by a rebound increase in ultrafiltrate concentrations, which means that its effect may not be clinically relevant, as total clearance by the filter for the dosage interval remains unchanged.

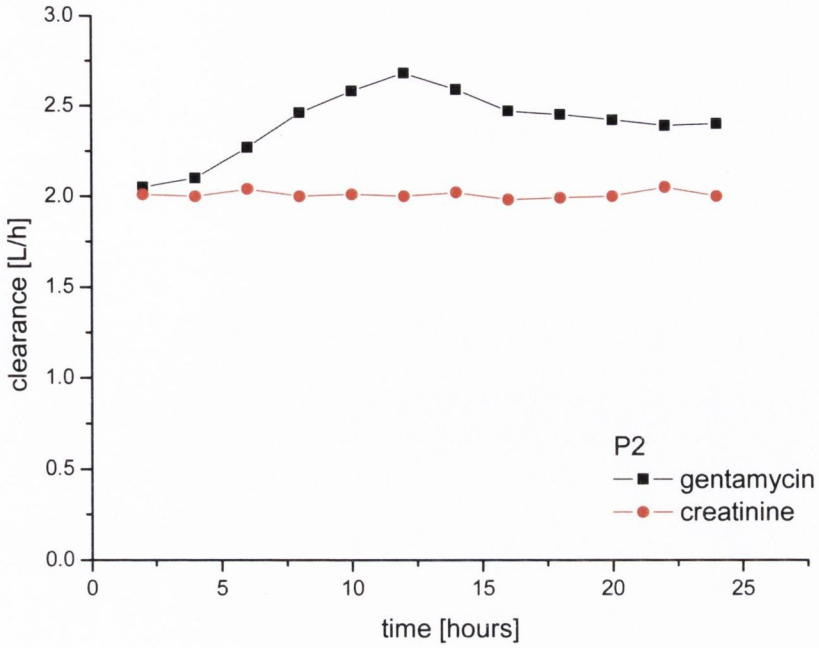


Figure 5.6.2: Comparison of Gentamicin and Creatinine Clearances over time during CVVHDF for Patient 2.

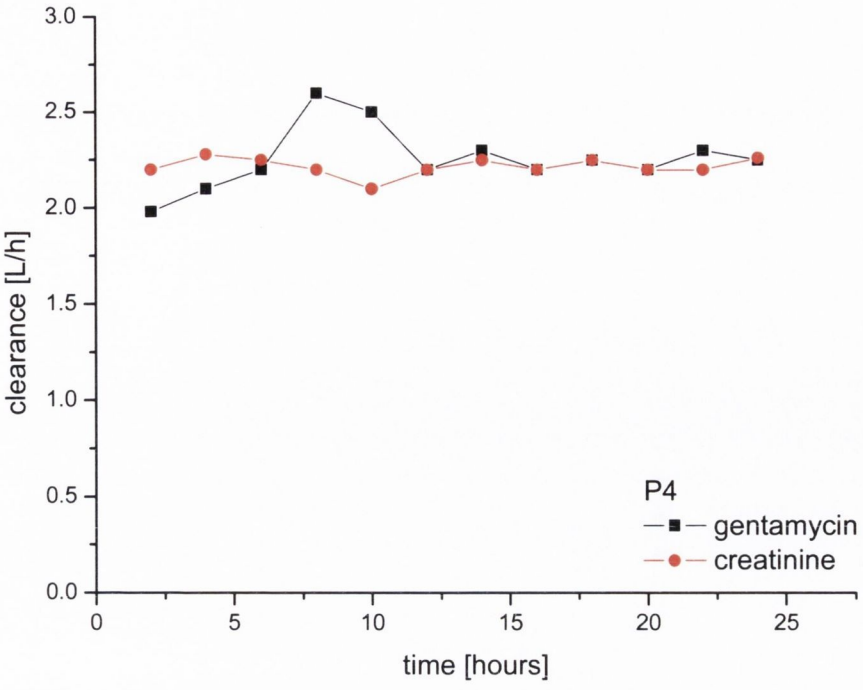


Figure 5.6.3: Comparison of Gentamicin and Creatinine clearances by CVVHDF therapy over time for Patient 4.

For all other patients, clearance of both creatinine and gentamicin remained constant over time. Prior to the relevant profiles in Patients 2 and 4, filter changes had occurred. This phenomenon was investigated further in the treatment of Patient 7. Prior to administering dose '7B', the filter was changed. Effluent fluid and serum concentrations were monitored over two dosage intervals. For the first dosage interval, 7B, the trend of a slight increase in gentamicin clearance over time was again observed, but for profile 7C, where the existing filter remained in use, gentamicin clearance was relatively constant over the dosage interval. Figure 5.6.5 compares gentamicin clearance over time in Patient 7 for pharmacokinetic profiles 7B and 7C.

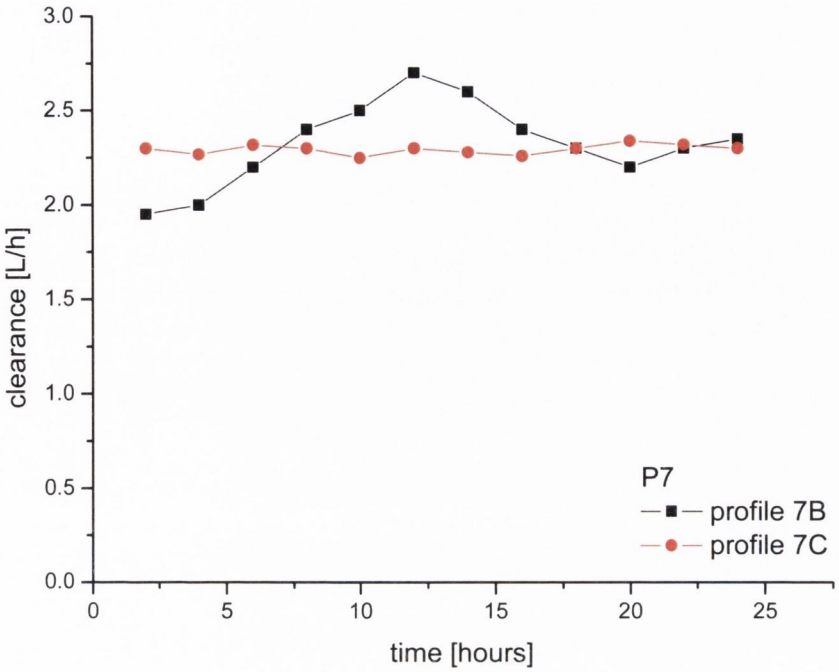


Figure 5.6.4: Gentamicin clearance due to CVVHDF over time for two dosage intervals for Patient 7.

5.7 Aminoglycoside Clearance due to CVVHDF

The mean clearance of gentamicin due to CVVHDF was 2.3 +/- 0.3 L/hr. This is 82% of the total body clearance of gentamicin and the sieving coefficient was 0.85 +/- 0.05. The mean clearance of amikacin was 2.9 +/- 0.4 L/hr, which was 91% of the total body clearance. The sieving coefficient for amikacin was 0.83 +/- 0.05. The difference in gentamicin clearance versus amikacin clearance may relate to differences in CVVHDF conditions, particularly effluent fluid flow rates. The mean effluent flow rate achieved among the patient sample concurrently treated with gentamicin and CVVHDF was 2.71 L/hr, while the mean flow rate achieved during amikacin therapy was 3.53 L/hr. This is reflected in differences in the observed creatinine clearance among the two samples. The mean creatinine clearance among the sample treated with gentamicin was 2.22 +/- 0.39, while the creatinine clearance among the amikacin sample was 2.7 +/- 0.4 L/hr. The estimated sieving coefficients were similar for both drugs and for creatinine among both samples, so the variability in the observed clearance may be explained by changed in the effluent flow rates.

According to the SPC for amikacin (Amikin) (227), twenty per cent or less is bound to plasma protein and so the unbound fraction is likely to be similar to the observed sieving coefficient of 0.83 +/- 0.05. According to its SPC, gentamicin (Genticin) (227) is less than 10% bound to protein and so the estimated sieving coefficient appears to be slightly less than the unbound fraction.

However, there is a possibility that there is some adsorption of gentamicin to the filter, which may explain the discrepancy between the reported level of protein binding and the observed sieving coefficient.

Chapter 6. Ciprofloxacin Pharmacokinetics in Critically Ill Patients Treated with CVVHDF

6.1 Introduction

6.1.1 Ciprofloxacin: A Fluoroquinolone Antibiotic

Ciprofloxacin is a broad-spectrum anti-infective agent of the fluoroquinolone class. Quinolones rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type 4 topoisomerase, resulting in rapid bacterial death. As a general rule, gram-negative bacterial activity correlates with inhibition of DNA gyrase, and gram-positive bacterial activity corresponds with inhibition of DNA type 4 topoisomerase (228,229).

Quinolones can be divided into four classes with each class adding coverage for a new group of pathogens. Ciprofloxacin is a second generation quinolone or 'fluoroquinolone'. These agents have improved pharmacokinetics versus first generation agents and are effective against a wide variety of bacteria and mycobacteria. The fluoroquinolones exhibit increased gram-negative and systemic activity. Fluroquinolones are also effective against Staphylococcus aureus, although resistance of S. aureus to the quinolones has been reported (230-232). In critically ill patients, severe urinary or gastrointestinal tract infections as well as ventilator-associated pneumonias are typical indications for ciprofloxacin.

6.1.2 Pharmacodynamic properties

Like the aminoglycosides, the quinolones exhibit concentration-dependent bacterial killing (231-234). Bactericidal activity becomes more pronounced as the serum drug concentration increases to approximately 30 times the minimum inhibitory concentration (MIC). Quinolones have a postantibiotic effect and

organisms may not resume growth for 2-6 hours after exposure to ciprofloxacin despite undetectable drug levels. The goal of therapy is to maximise serum AUC and the PK/PD parameters that are indicators of efficacy are 24-hr AUC/MIC and peak/MIC ratios (233).

There is general concern about the emergence of resistance as a result of inadequate doses of ciprofloxacin (234). Pathogens are generally regarded as sensitive to ciprofloxacin if their MIC is less than 1mg/L and resistant if the MIC is greater than 4mg/L (SPC). A C_{pmax}/MIC ratio of 8 and an AUC_{24}/MIC > 125 have been proposed as indicators of therapeutic efficacy (235-237).

6.1.3. Adverse effects

Fluoroquinolones are considered to be safe and well-tolerated (238-241), although there are some notable exceptions, for example, temafloxacin and grepafloxacin (242-244). Most adverse effects caused by fluoroquinolones are comparable, although frequency and manifestation of certain adverse effects differ among agents (241-245). The events are typically mild and usually resolve during continued treatment or with discontinuation of therapy. Gastrointestinal effects and CNS effects are most common. Gastrointestinal effects do not appear to be related to or affected by structural changes in the fluoroquinolone nucleus (245,246). They are thought to be caused by a combination of direct GI irritation and CNS-mediated effects (246); thus some may occur with IV administration.

The estimated overall frequency of GI effects is 2-20% and they are the most commonly reported adverse effects for fluoroquinolones (239, 240, 245, 246,247).

CNS side-effects are the second most common group of adverse effects associated with the fluroquinolones. Their overall frequency is 1-2% and these

may include headache, dizziness, drowsiness and rarely insomnia, restlessness and vision changes (240,245).

CNS effects of fluroquinolones may result from direct effects or from drug-drug interactions. Fluroquinolones can also cause dermatological adverse effects, most notably phototoxic reactions (246). Liver enzyme abnormalities occur in 2-3% of patients who receive fluoroquinolones (248). Nephrotoxic effects of the fluoroquinolones are uncommon, although rare cases of haematuria, interstitial nephritis, and acute renal failure were reported (245,248).

6.1.4 Drug-Drug Interactions

All fluoroquinolones interact with multivalent cation-containing products, such as aluminium-or magnesium- containing antacids and products containing iron, calcium or zinc. Concomitant use invariably reduces oral absorption of the antibiotic, through the formation of insoluble chelation complexes in the GIT that inhibit absorption (249). This increases the risk of therapeutic failure. Multivitamin preparations that contain minerals and ferrous sulphate have been shown to decrease the bioavailability of fluoroquinolone antibiotics from 19-66% (250-253). Sucralfate significantly interferes with oral absorption of fluroquinolones, reducing bioavailability by up to 98% when given within two hours of the antibiotics (254, 255). This will be of major significance, if critically ill patients are taking an oral fluoroquinolones and sucralfate, which was prescribed for a small number of patients in the retrospective audit. Proper timing of drug administration may minimise these interactions in the GIT.

Fluoroquinolones can inhibit clearance of xanthine derivatives, such as theophylline and caffeine. The relative inhibitory capacity of individual antibiotics depends on the specific affinity of each fluoroquinolone for the cytochrome P450 isozyme 1A2 (256).

In numerous studies, ciprofloxacin decreased theophylline clearance by 25-30% and increased theophylline plasma concentrations by as much as 30%. Inhibition of certain cytochrome P450 enzymes by fluoroquinolones can result in decreased warfarin metabolism and increased therapeutic response. Ciprofloxacin caused an increase in serum phenytoin when administered concurrently (257).

6.1.5 Clinical Pharmacokinetics

Quinolones are well absorbed following oral administration and serum drug levels obtained are comparable with those obtained after intravenous administration, thus facilitating an early po to iv switch. Quinolones are widely distributed throughout the body. Tissue penetration is high and for this reason ciprofloxacin is commonly used to treat peripheral compartment infections (78,79). Protein binding is low (between 19-40%). Ciprofloxacin is present in plasma largely in a non-ionised form. Ciprofloxacin distribution to the extravascular space is extensive and this is reflected by the large volume of distribution and the high concentrations of ciprofloxacin in extravascular fluids and tissues. Ciprofloxacin pharmacokinetics have been described by a two- and three- compartment model (258-263), in addition to noncompartmental methods (261,263). An advantage of noncompartmental analysis is that it requires fewer assumptions than that which is necessary with compartmental analysis. For example, LeBel et al (261) found that serum concentrations were best described by a triexponential equation for ten of twelve patients but by a biexponential equation for the remaining two patients, in a study of ciprofloxacin pharmacokinetics and blister fluid penetration. Drusano et al (258) also found that a 2-compartment model gave a good fit for some patients but that a 3-compartment model was required for other patients. The use of

noncompartmental methods avoids this issue. Some studies have used a combination of compartmental and model-independent methods (261).

Ciprofloxacin elimination occurs via several organs of elimination. Since blood is fractionally distributed to various potential organs of elimination in parallel, the clearance of drug from the various organs of elimination is additive.

In patients with normal renal function, the major route of ciprofloxacin elimination is via the kidneys. After intravenous doses of ciprofloxacin, 75% of the dose is eliminated by the kidneys and 14% in the faeces within 5 days. Renal elimination takes place mainly during the first 12 hours after dosing and renal clearance levels suggest that active secretion by the renal tubules occurs in addition to normal glomerular filtration. The elimination kinetics are linear and after repeated dosing at 12 hourly intervals, no further accumulation is detected after the distribution equilibrium is attained (at 4-5 half-lives). The elimination half-life of unchanged ciprofloxacin over a period of 24-48 hours post-dose is 3.1-5.1 hours. Thus, the half-life is approximately 4 hours in patients with normal renal function and doubles in patients with severe renal impairment. Drusano et al (258) demonstrated a good correlation between normalised creatinine clearance and both normalised serum and renal clearance. Biotransformation to four metabolites, in addition, contributes to removing the compound from the body (10-20%). Four different antimicrobially active metabolites have been reported; desethyleneciprofloxacin, sulphociprofloxacin, oxaciprofloxacin and formylciprofloxacin. Sulphociprofloxacin and oxaciprofloxacin account for one third each of metabolised substance and desethyleneciprofloxacin is found in small amounts (1.3-2.6% of the dose). Formylciprofloxacin has been found in very small quantities (<0.1% of the dose).Transintestinal elimination of ciprofloxacin has been reported as an

additional extrarenal route of elimination, particularly as a compensatory route in patients with renal dysfunction (264). Drusano et al (258) reported serum clearances (mean +/- s.d) of 26.8 +/- 5.7 and 15.4 +/- 4.3 L/hr per 1.73 m^2 in normal and anephric volunteers respectively.

6.1.6 Ciprofloxacin pharmacokinetics during critical illness and CVVHDF

The pharmacokinetics of ciprofloxacin is affected by critical illness and the presence of organ failure and dosage adjustment is often recommended in such situations. In patients with severely impaired renal function, a 50% dosage reduction is recommended by the manufacturer (Bayer, SPC). There is widely varying reports in the literature on ciprofloxacin pharmacokinetics during critical illness, with data extrapolated from stable patients with renal failure and from critically ill patients without renal failure.

Consequently, the current dosage guidelines for ciprofloxacin during critical illness vary extensively. Doses ranging from 200mg twice daily to 400mg three times daily have been used for critically ill patients without renal impairment (265,266). In ICU patients with renal failure, a range of doses from 200mg daily to 200mg four times daily have been suggested (267,268). Shah et al (269) used 300mg twice daily in patients with renal impairment (creatinine clearance < 30ml/min) not receiving dialysis. Davies et al (143) used 200mg twice daily initially but increased this to 200mg three times daily midway through the study, on observing that the initial regimen failed to achieve adequate serum concentrations. Cotterill et al (141) recommended 200mg every twelve hours for patients treated with CVVH.

Large interpatient variation has been found in ciprofloxacin pharmacokinetics during hemofiltration and hemodiafiltration. A number of small studies with small numbers or case reports (143,270) have examined the effect of less

efficient forms of RRT on ciprofloxacin pharmacokinetics. A dose of 400mg twice daily, despite the manufacturer's recommendations, was suggested by Jones et al (271) for critically ill patients with renal insufficiency, unless they have concomitant bowel or liver disease, irrespective of whether they were on CVVH or not. In the study by Jones et al, peak and trough concentrations were monitored in 11 patients on haemofiltration. However, details of the haemofiltration process were not reported, which makes extrapolation of the results to our patients treated with CVVHDF difficult. Recently, Wallis et al (6) reported on six critically ill patients treated with CVVHDF and a ciprofloxacin dosing schedule of 200mg every 8 hours, which is less than the dosing regimen commonly prescribed in this ICU. Malone et al (272) examined ciprofloxacin and levofloxacin pharmacokinetics in patients treated with CVVH (5) and CVVHDF (5), and concluded that 400mg/day was adequate to maintain therapeutic concentrations. Bellmann et al (273) investigated ciprofloxacin pharmacokinetics in eight patients treated with CVVH and five patients not treated with CVVH. The membrane in use was a polysulfone membrane, which differed from the membrane used in this study (polyacrylonitrile membrane) and the renal replacement therapy technique was haemofiltration rather than haemodiafiltration. As a result of the reported variability in ciprofloxacin pharmacokinetic parameters during critically illness, differences in patients' case mix and CRRT conditions and the absence of a consensus on dosing regimens, a prospective pharmacokinetic evaluation of ciprofloxacin during CVVHDF therapy was undertaken.

6.2 Prospective Pharmacokinetic and Clinical Evaluation of Ciprofloxacin during Critical Illness and CVVHDF therapy

6.2.1 Patient Demographics and Clinical Characteristics

Seven critically ill patients, treated concurrently with intravenous ciprofloxacin and CVVHDF therapy, were enrolled in the study. Demographic and clinical data are presented in Table 6.2.1.

Table 6.2.1: Patient Demographics and Clinical Characteristics

ID	Sex	Age	Diagnosis	Infective Diagnosis	APACHE II Score[1]	SOFA Score[2]	SrCr[3]	Cr Cl[4]	CVVHDF Duration (days)
1	M	60	Intestinal obstruction 2y caecal tumour, Hemicolectomy Cirrhosis, alcoholic liver disease	Escherichia coli, S. aureus, Candida albicans	26	9	124	6	6
2	F	77	Neutropenic sepsis, ARF, metastatic lung cancer	Pseudomonas aeruginosa Coagulase negative staphyloccoi, MRSA	27	5	92	6	5
3	F	68	Emergency Hartman's procedure for Colonic obstruction, post-op acute renal failure and sepsis, anuric	Enterococcus faecalis, Pseudomonas aeruginosa, MRSA	28	4	130	8	14
4	M	47	Acute pancreatitis, Septicaemia, Bilateral pneumonia, Pulmonary oedema, Pyrexia, pleural effusion	Escherichia coli MRSA.	25	10	168	4	14
5	F	71	Acute on chronic renal impairment, ESRD, Sepsis	Empiric cover	27	9	407	2	8
6	M	57	Cirrhosis of liver, Acute renal failure, severe sepsis, thrombocytopenia,	Actinetobacter baumanni, Enterococcus Faecalis, Pseudomonas aeruginosa,	29	11	120	5	7

			coagulopathy, metabolic acidosis, anuric	Coagulase negative staphylococci					
7	M	28	Acute Liver Failure with hepatic encephalopathy, ARF, coagulopathy, ascites.	Enterobacteriaceae P. aeruginosa S. aureus	30	12	113		11

[1, 2] Initial/ICU admission values
[3] Measured on day 1 of CVVHDF, prior to its commencement Units = µmol/L.
[4] Measured on day 1 of CVVHDF, prior to its commencement Units = ml/min; estimated using the method of Jeliffe and Jeliffe (42).

Six patients were prescribed ciprofloxacin for documented infection, while one patient with suspected sepsis was prescribed ciprofloxacin empirically. Four patients were treated for infections caused by Pseudomonas aeruginosa, two for infections caused by Escherichia coli and one for infection due to Enterobacteriaceae species. Five patients had infections due to staphylococcus aureus. Two patients were MRSA positive. One patient (patient 5) had received oral ciprofloxacin within the fortnight prior to their admission to ICU.

The mean APACHE Π score was 27.43 +/- 1.72. The mean SOFA score was 8.57 +/- 2.99. All patients had severe renal impairment. Four patients had concurrent hepatic dysfunction.

The mean duration of CVVHDF therapy was 9.3 +/- 3.7 days. The mean effluent flow rate achieved was 3.3 +/- 0.5 L/hr (Range: 2.9 – 4.0 L/hr). The dialysate rate prescribed was either 1L/hr or 2L/hr and the ultrafiltrate rate prescribed was 2L/hr. For patients 6 and 7, CVVHDF was run heparin-free.

6.2.2 Measurement of Ciprofloxacin Concentrations

Ciprofloxacin concentrations in serum and effluent samples were measured by the HPLC method of Davis et al (74), adapted for both serum and effluent fluid analysis.

(1) Quantitation

Quantitation was based on external standard calibration using the ratio of the peak areas of the analyte and the internal standard. For the quantitation of serum samples, spiked serum with analyte concentrations between 0.1 and 20.0 μg/ml was used for the calibration curve. Calibration curves for ultrafiltrates were generated by measuring ciprofloxacin standards in blank dialysis fluid in a concentration range of 0.1 -20 μg/ml. The within- and between-day accuracy and precision were calculated by measuring spiked serum samples and ciprofloxacin standards in phosphate buffer at three different concentrations in triplicate on three different days. The accuracy was calculated as the percentage of the determined concentration form the nominal ones. The precision was given as the relative standard deviation (R.S.D. %). The limit of detection was given as determined by a signal-to-noise ratio of 3. Ciprofloxacin recovery from control blood was determined by slope comparison of extracted and non-extracted calibration curves. Replicate analysis was preformed both on control samples and study samples to eliminate batch variations.

(2) Validation

Ciprofloxacin hydrochloride monohydrate (1g) was obtained as a gift from Bayer UK. This was used to verify the concentration of the commercial infusion solution Ciproxin. The mean concentration was found to be 1.96 +/- 0.5mg/ml (n=5).

When plotting the peak: height ratio of ciprofloxacin to β-hydroxypropyl theophylline against the known amount of ciprofloxacin in controlled serum samples (range 0.2 – 20.0μg/ml), a linear relationship was observed. Linearity was also observed when analysing ciprofloxacin in dialysis fluid samples over the concentration range investigated (0.2 – 20.0μg/ml). The extraction efficiency was found to be in excess of 80% (80.1 – 87.6% over the concentration range 0.5-20μg/ml). The within-day variability was good – the coefficient of variation was less than 12% over the concentration range studied. The between day coefficient of variation was less than 10%. The precision was less than 5.0 R.S.D %. The sensitivity of the assay was found to be 0.5μg/ml.

Table 6.2.2: Extraction efficiency for ciprofloxacin

Concentration (mg/L)	**Recovery (mean +/- S.D.) (%)**
0.5	81.2 +/- 11.2
1.0	79.9 +/- 9.2%
2.0	82.3 +/- 8.6%
5.0	89.8 +/- 9.8%
10.0	91.2 +/- 6.2%
20.0	88.7 +/- 7.2%

Table 6.2.3: Within-day and between day variability (coefficient of variation %) and precision for the determination of ciprofloxacin in spiked serum samples.

Concentration (mg/L)	Within-day variability (C.V. %) (n=3)	Between-day variability (C.V. %) (n=9)	Within-day Precision (R.S.D. %)	Between-day Precision (R.S.D. %)
1.0	12.1	10.2	1.45	2.10
5.0	11.2	13.3	1.55	1.46
10.0	10.8	13.8	0.95	0.98

Table 6.2.4: Within- and between-day variability and precision for the determination of ciprofloxacin in dialysis fluid.

Concentration (mg/L)	Within-day variability (C.V. %)) (n=3)	Between-day variability (C.V. %) (n=9)	Within-day Precision (R.S.D. %) (n=3)	Between-day Precision (R.S.D %) (n=9)
0.2	10.6	11.1	2.56	2.80
1.0	9.8	11.3	3.21	2.94
5.0	8.6	9.3	3.46	3.55
10.0	8.9	9.0	1.86	1.43

The stability of ciprofloxacin was monitored at conditions necessary for sample treatment and measurement. Ciprofloxacin standard solutions were incubated at 37 degrees Celsius for 1 hour and were reanalysed after 24 hours stored in the autosampler tray at 10 degrees Celsius. Additionally, ciprofloxacin standard solutions were stored at -20 degrees Celsius for 1, 2, 3 and 4 months and reanalysed. The concentration changes are within the accuracy of the assay. This is in accordance with the literature where solutions of ciprofloxacin have been reported to be stable at -20 degrees Celsius for at least 4 months and the

SPC data (227), which reports stability for the in-use period and for 24 hours when stored at temperatures < 25 degrees Celcius. Stability data of ciprofloxacin are given in Table 6.2.5 below.

Table 6.2.5: Stability of ciprofloxacin in phosphate buffer after incubation at 37 degrees Celsius for 1 hour and after storage at 10 degrees Celsius for 24 hours.

Concentration (mg/L)	**0.5**	**1**	**2**	**5**
Percentage of original concentration after incubation at 37 degrees Celcius for 1hr	100.3	99.8	101.4	103.2
Percentage of original concentration after storage at 10 degrees Celcius for 8 hrs	99.4	100.2	99.8	100.5

6.2.3 Analysis of Serum Concentrations of Ciprofloxacin

Seventeen pharmacokinetic profiles were obtained from these seven patients. For each dosage interval for each patient, a minimum of seven serum samples were obtained. The ciprofloxacin serum concentration – time data are presented in Figures 6.2.1- 6.2.7.

Figure 6.2.1 presents the ciprofloxacin serum concentration-time data for Patient 1, following administration of a 400mg dose of ciprofloxacin, infused intravenously over 60 minutes. The dosage interval was 12 hours. The first serum concentration was measured immediately before the infusion was started and further concentrations were monitored immediately after the infusion finished and at 2, 3, 4, 6, 8 and 12 hours after the infusion start time. There was a slight increase in the trough concentration at the end of the second dosage interval studied, although the same dosing schedule was maintained. Cpmax concentrations achieved by both profiles were similar, as were the AUC_{0-12} measurements (Table 6.2.6).

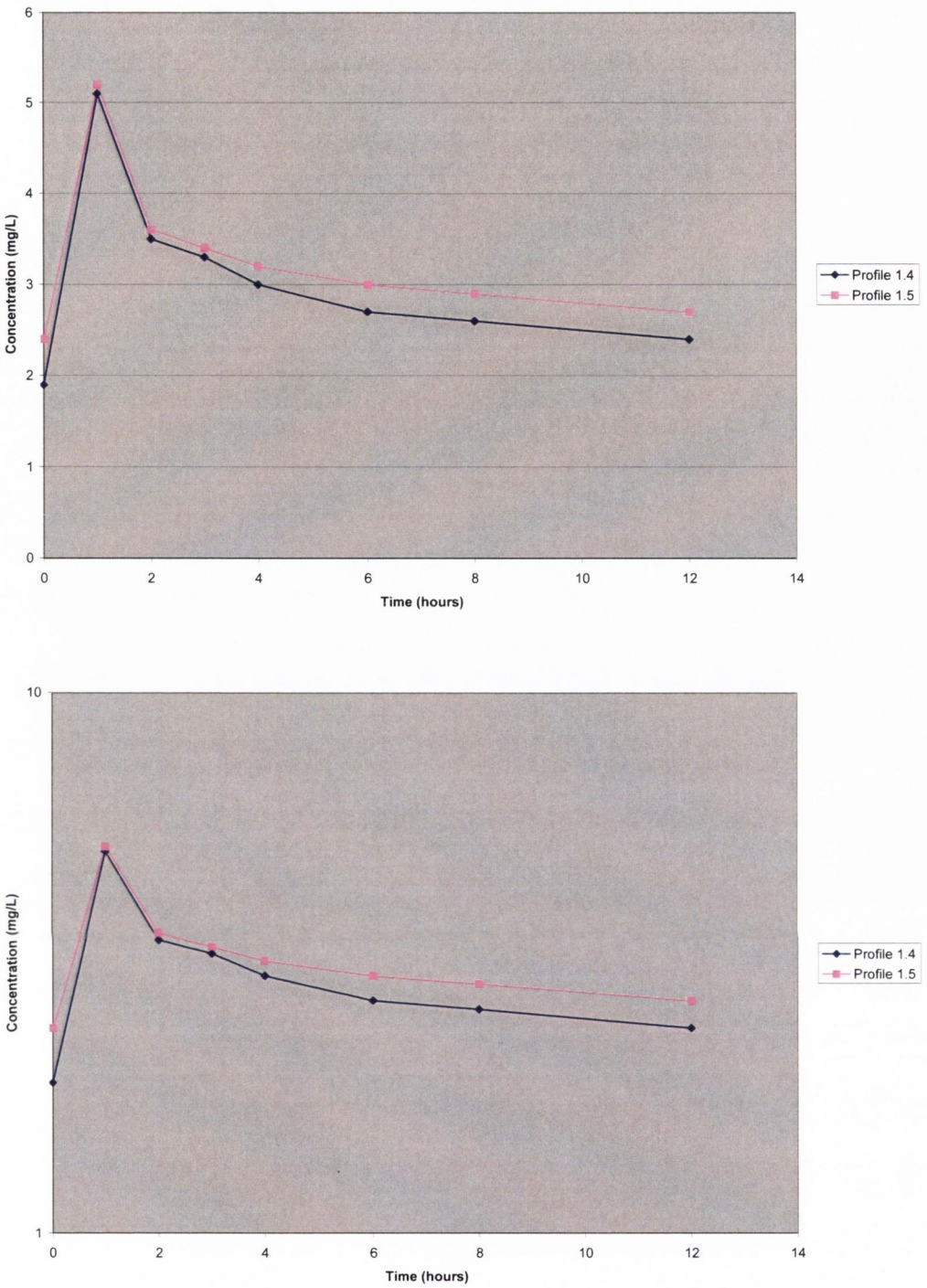


Figure 6.2.1: Ciprofloxacin serum concentration-time data for Patient 1 (linear and semi-log plots)

Figure 6.2.2 presents the ciprofloxacin serum concentration-time data for Patient 2, following administration of a 200 mg dose of ciprofloxacin, infused intravenously over 60 minutes. The dosage interval was 12 hours.

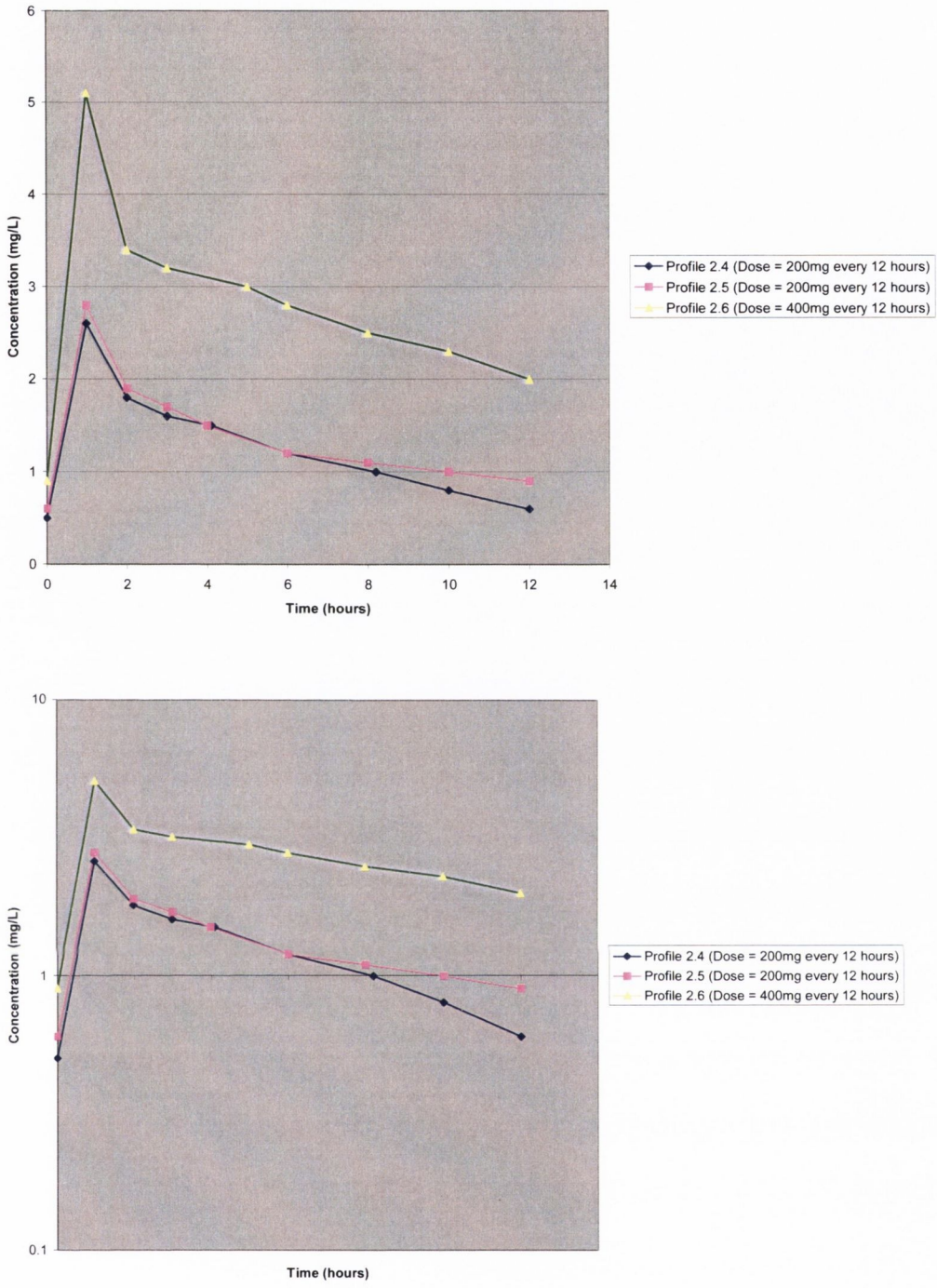


Figure 6.2.2: Ciprofloxacin serum concentration-time data for Patient 2 (linear and semi-log plots)

Ciprofloxacin serum concentrations were measured over the same timeframe as for patient 1. However, there was some variability in the exact sampling times used for each pharmacokinetic profile. For profile 2.4, serum samples were taken at 4.1 and 8.2 hours rather than 4.0 and 8.0 hours. For profile 2.6, a serum

sample was taken at 5.0 hours rather than 4.0 hours. Similar Cpmax concentrations were achieved for the first two pharmacokinetic profiles, where a dosing schedule of 200mg every 12 hours was administered. On the basis of a MIC value of 0.5mg/L; the C_{pmax}/MIC ratio was approximately 5, which is less than the 8-10 proposed for optimal microbiological and clinical response. An increased dose of 400mg every 12 hours resulted in a higher C_{pmax} concentration (5.1mg/L), equivalent to a C_{pmax}/MIC ratio of about 10. Although the trough concentrations increased slightly with each dosage interval, given that the third profile followed a dosage increase, accumulation was not evident.

Figure 6.2.3 presents the ciprofloxacin serum concentration-time data for Patient 3, following administration of a 400 mg dose of ciprofloxacin, infused intravenously over 60 minutes. The dosage interval was 12 hours. Ciprofloxacin serum concentrations were measured immediately prior to starting the infusion, midway through the infusion (0.5hr), immediately after the infusion was complete (1.0 hr) and at 2, 3, 4, 6, 8, 10 and 12 hours. C_{pmax} and AUC_{0-12} measurements were consistent for both dosage intervals. There was a slight increase in the trough concentrations; this may be indicative of some degree of accumulation. The C_{pmax} concentrations achieved represented a C_{pmax}/MIC ratio of almost 13, which is above the target seen as indicative of adequate ciprofloxacin dosing (>10). The AUC_{0-24} /MIC ratio (=152) was also greater than the minimum target predictive of clinical response (>125).

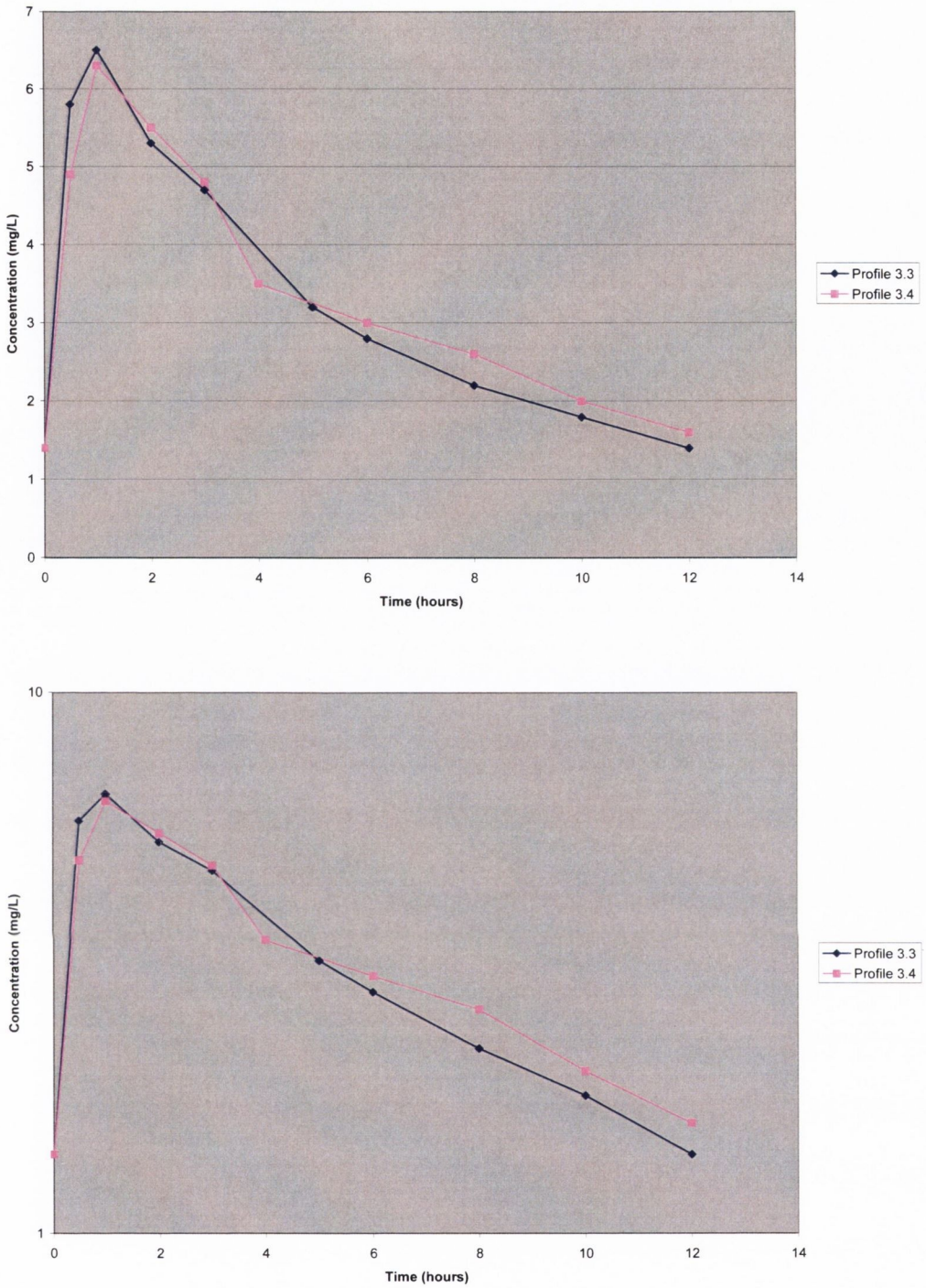


Figure 6.2.3: Ciprofloxacin serum concentration-time data for Patient 3 (linear and semi-log plots)

Figure 6.2.4 displays the ciprofloxacin serum concentration-time data for Patient 4. Profile 1 was obtained following administration of a 400 mg dose of ciprofloxacin, infused intravenously over 60 minutes. The dosage interval was 24 hours. For the second profile, the dosage interval was 12 hours. A serum

concentration measurement prior to administering ciprofloxacin was not available for the first pharmacokinetic profile as it followed the initial ciprofloxacin dose. Ciprofloxacin serum concentrations were measured immediately after the infusion was complete (1.0 hr) and at 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours for each profile.

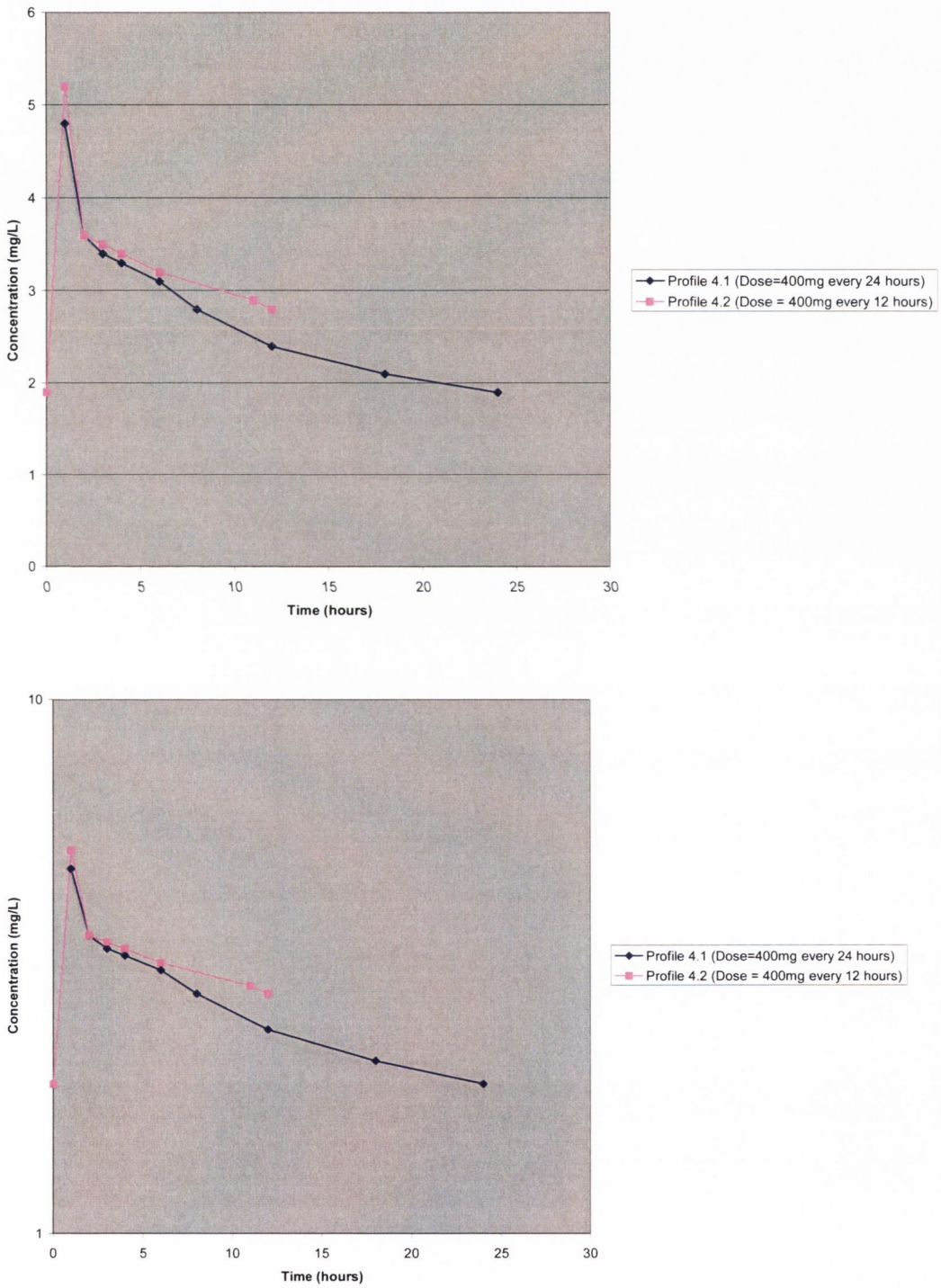


Figure 6.2.4: Ciprofloxacin serum concentration-time data for Patient 4 (linear and semi-log plots)

Following the first dosage interval, the dosage interval was reduced to 12 hours. The impact of the dosage change prior to achieving steady state conditions complicates its interpretation. Predictably, increases in C_{pmin} and C_{pmax} concentrations were observed. The estimated elimination rate constant and TBC were higher during the second dosage interval.

Figure 6.2.5 displays the ciprofloxacin serum concentration-time data for Patient 5, following administration of multiple doses of 400 mg ciprofloxacin, infused intravenously over 60 minutes. The dosage interval was 12 hours. Ciprofloxacin serum concentrations were measured immediately prior to starting the infusion, midway through the infusion (0.5hr), immediately after the infusion was complete (1.0 hr) and at 2, 3, 4, 6, 8, 10 and 12 hours. There was no consistent increase in C_{pmax} or C_{pmin} concentrations over time and accumulation was not evident. C_{pmax}/MIC and AUC_{0-24} were more than adequate, with mean values of approximately 14 and x respectively. Given that accumulation was not observed, the high dose tolerability of ciprofloxacin and the risk of resistance associated with inadequate ciprofloxacin concentrations, maintaining this dosing schedule, where high serum concentrations were achieved seems reasonable. The mean elimination half-life in this patient was 5.1 hours and the mean TBC was 11.2 L/hr. This patient had severe renal impairment but no hepatic dysfunction.

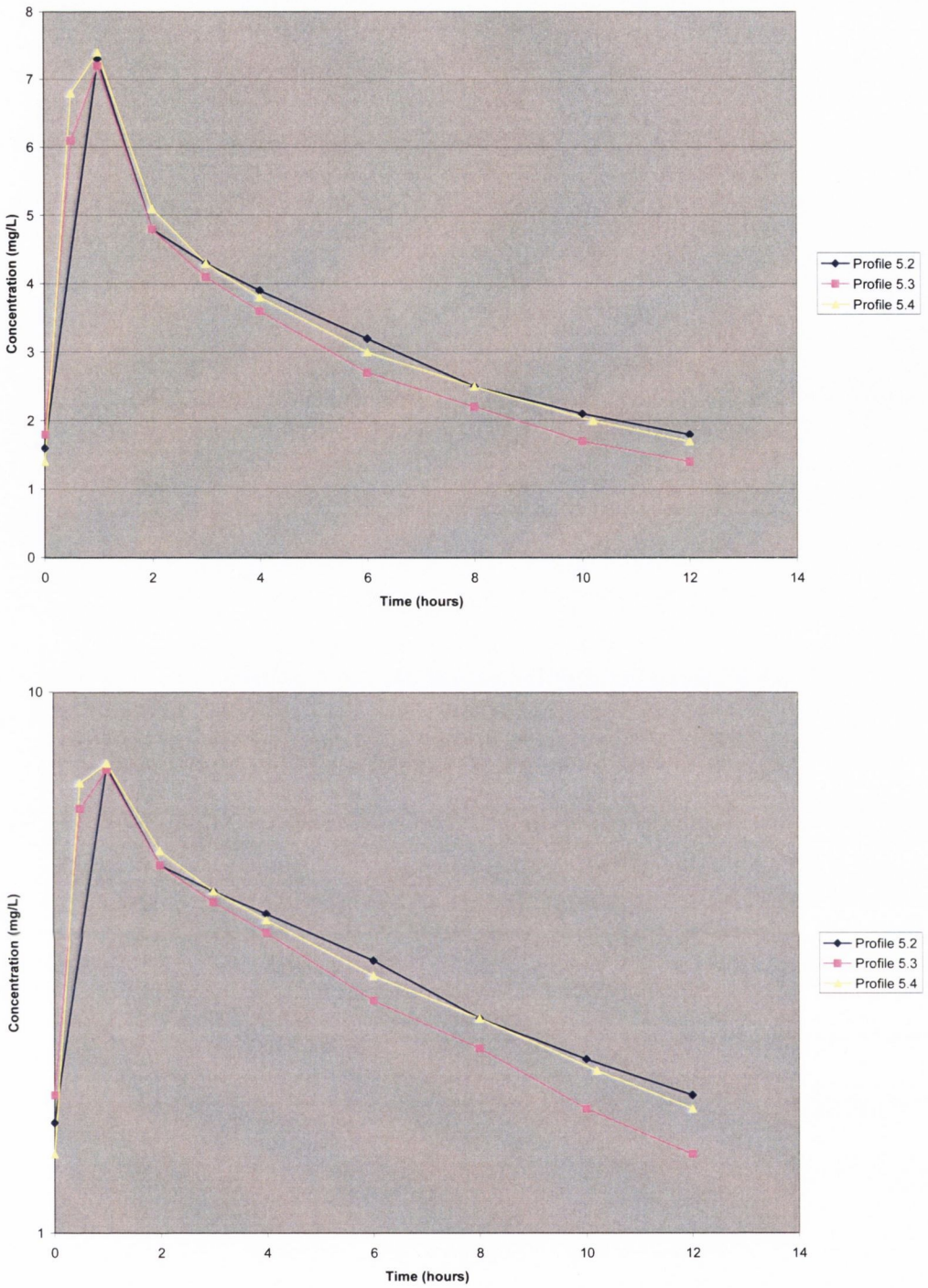


Figure 6.2.5: Ciprofloxacin serum concentration-time data for Patient 5 (linear and semi-log plots)

Figure 6.2.6 displays the ciprofloxacin serum concentration-time data for Patient 6, following administration of a 400 mg dose of ciprofloxacin, infused intravenously over 60 minutes. For the first pharmacokinetic profile, the dosage interval was 24 hours. For the second profile, the dosage interval was reduced to

12 hours. Ciprofloxacin serum concentrations were measured immediately prior to starting the infusion, immediately after the infusion was complete (1.0 hr) and at 2, 3, 4, 6, 8 and 12 hours.

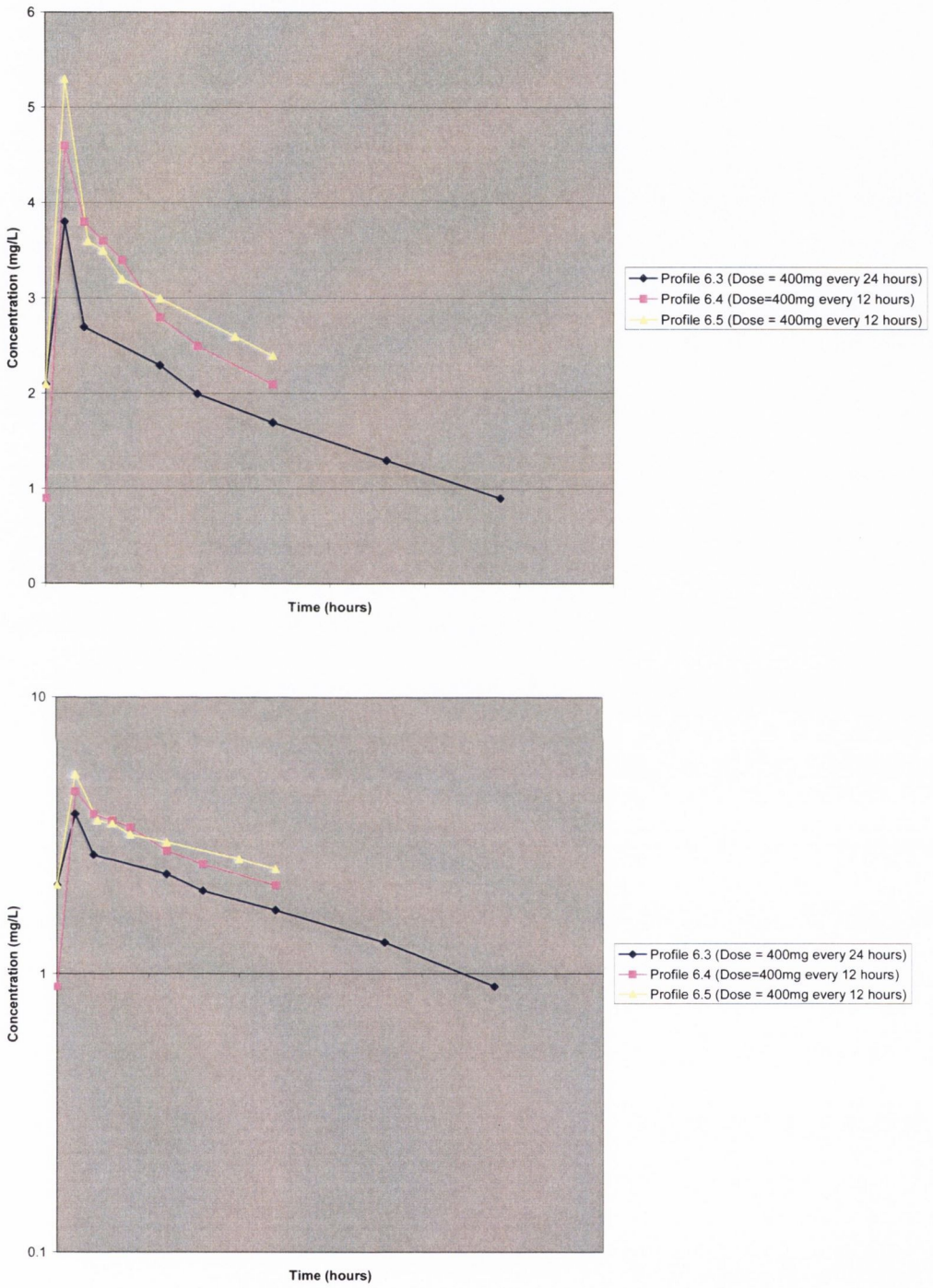


Figure 6.2.6: Ciprofloxacin serum concentration-time data for Patient 6 (linear and semi-log plots)

Figure 6.2.7 displays the ciprofloxacin serum concentration-time data for Patient 7, following administration of a 400 mg dose of ciprofloxacin, infused intravenously over 60 minutes. The dosage interval was 24 hours for the first profile and 12 hours for the second profile. Ciprofloxacin serum concentrations were measured immediately prior to starting the infusion, immediately after the infusion was complete (1.0 hr) and at 2, 3, 4, 6, 8 and 12 hours.

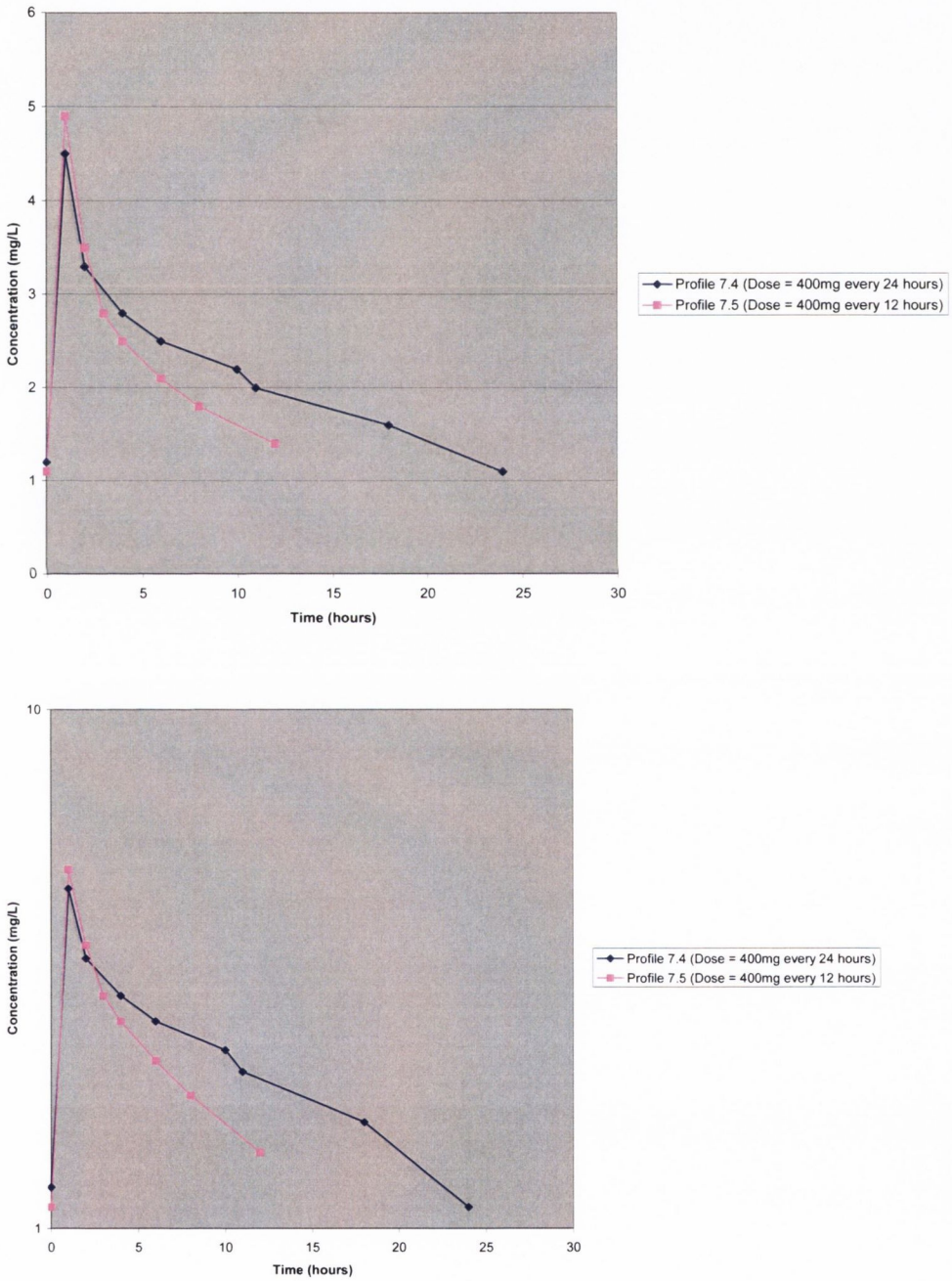


Figure 6.2.7: Ciprofloxacin serum concentration-time data for Patient 7 (linear and semi-log plots)

6.3 Pharmacokinetic Discussion:

The ciprofloxacin serum concentration – time profiles for the seven patients are graphically represented in Figure 6.3.1.

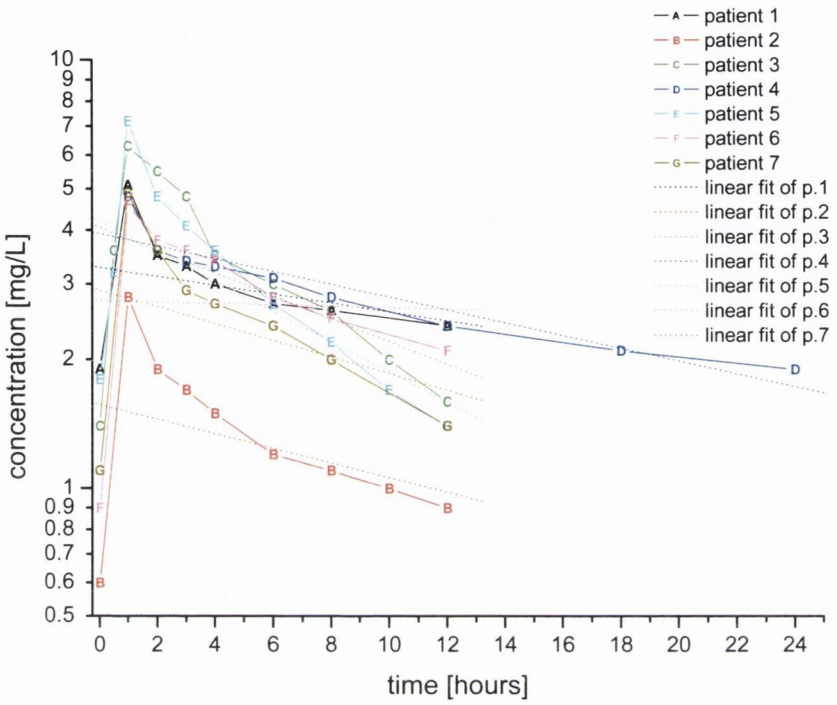


Figure 6.3.1: Ciprofloxacin serum concentration – time data for critically ill patients treated with CVVHDF

The ciprofloxacin pharmacokinetic parameters estimated for each patient pharmacokinetic profile during treatment with CVVHDF are presented in Table 6.3.1. C_{pmax} was directly observed as the measured concentration. Noncompartmental pharmacokinetic methods were used. The terminal half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. The area under the plasma concentration-time curves (AUCs) were calculated using the linear trapezoidal method. AUC for the study period (n =12 or 24 hours) was used to calculate the AUC extrapolated to infinity ($AUC_{0-\infty}$) by the equation $AUC_{0-n} + C_n/\lambda_z$. The TBC was calculated as dose/ $AUC_{0-\infty}$ for initial doses and as dose/ AUC_{0-n} for subsequent doses.

Volume of distribution at steady state was calculated as Vd_{ss} = Dose x (AUC_{0-12} + (12 X C_{12}/ λ_z))/(AUC_{0-12})^2.

Table 6.3.1: Estimates of pharmacokinetic parameters obtained from multiple ciprofloxacin serum concentrations in a dosage interval using non-compartmental methods:

Patient Profile	Dose (mg)	Dosage Interval (hours)	$t_{1/2}$ (hrs)	K (hr^{-1})	AUC_{0-n} (n=dosage interval) (mg.hr/L)	TBC (L/hr)	Vd_{ss} (L)
1.4	400	12	10.11	0.068	32.9	12.15	178.79
1.5	400	12	11.63	0.059	38.6	10.36	175.59
Mean			**10.87**	**0.064**	**35.8**	**11.26**	**177.19**
2.4	200	12	5.20	0.133	12.4	16.13	121.28
2.5	200	12	6.72	0.103	13.3	15.04	145.99
2.6	400	12	8.14	0.085	26.9	14.86	174.93
Mean			**6.69**	**0.107**	**17.5**	**15.34**	**147.40**
3.1	400	12	4.97	0.139	38.7	10.33	74.36
3.2	400	12	5.56	0.125	37.6	10.63	85.11
Mean			**5.27**	**0.132**	**38.2**	**10.48**	**79.94**
4.1	400	24	17.20	0.040	58.2	6.87	171.82
4.2	400	12	12.32	0.056	37.3	10.72	191.43
Mean			**14.76**	**0.048**	**47.8**	**8.80**	**181.63**
5.1	400	12	5.44	0.127	34.6	11.56	91.02
5.2	400	12	4.65	0.149	33.9	11.80	79.19
5.3	400	12	5.18	0.134	39.3	10.18	75.96
Mean			**5.09**	**0.137**	**35.9**	**11.18**	**82.06**
6.1	400	24	11.06	0.063	38.9	10.28	163.22
6.2	400	12	9.72	0.071	29.3	13.65	192.28
6.3	400	12	9.62	0.072	27.4	14.60	148.54
Mean			**10.13**	**0.069**	**31.9**	**12.84**	**168.01**
7.1	400	24	6.58	0.105	42.3	9.45	123.84
7.2	400	12	6.08	0.114	29.8	13.42	117.74
Mean			**6.33**	**0.110**	**36.1**	**11.44**	**120.79**

*Cpmax is the actual maximum serum concentration i.e. the concentration at the time point when the infusion was complete.

The mean elimination rate constant was 0.09 +/- 0.03 hr^{-1} and the half-life of ciprofloxacin ranged from 4.65 hours - 17.20 hours. The mean half-life was 8.2 +/- 3.5 hours. In patients with normal renal function, the major route of ciprofloxacin elimination is via the kidneys. The half-life of ciprofloxacin, approximately 4 hours in patients with normal renal function, doubles in

patients with severe renal impairment. The mean half-life observed during critical illness/ARF and treatment with CVVHDF in this study is similar to that reported for patients with severe renal impairment (8.7 +/- 0.9 hours). The half-life in patient 4 was further extended to 14.8 hours. This patient had acute pancreatitis and concomitant hepatic and renal dysfunction resulted in a prolonged half-life. The half-lives observed in patients 3 and 5 were close to those seen in patients with normal renal function. As illustrated by these examples, there was a high level of interpatient variability in the elimination half-life and the coefficient of variation was 42%.

The mean TBC of Ciprofloxacin was 11.88 +/- 2.42 L/hr. This value represented hepatic, residual renal and transintestinal ciprofloxacin clearance, in addition to ciprofloxacin clearance by the filter. A ciprofloxacin TBC range of 0.17 – 0.82 L/hr/kg has been reported for critically ill patients with normal renal function. For a patient weighing 70kg, this represents a range of 11.9 Lhr – 57.4 L/hr and so is greater than the ciprofloxacin clearance observed among this patient sample. Wallis et al (6) reported a similarly reduced ciprofloxacin clearance in 6 patients treated with 200mg tds during CVVHDF therapy (0.06 - 0.25 L/hr/kg). Ciprofloxacin clearance due to CVVHDF will be discussed in the next section.

The Vd for ciprofloxacin during CVVHDF therapy ranged from 74.4 – 192.3 L and the mean value was 135.95 +/- 42.85 L. This is similar to the range reported by Lipman et al (266) (0.77 – 2.52 L/kg or 57.8 L – 189 L, assuming a weight of 74kg) for critically ill patients treated with ciprofloxacin and that reported by Wallis et al (6) (135+/- 27 L) for six patients treated with 200mg every 8 hours.

The mean C_{pmax} concentration for the sample was 5.2 +/- 1.4 mg/L, with three dosing schedules prescribed; 200mg bd (n =2), 400mg od (n =3) and most

commonly 400mg bd (n =12). The mean trough (C_{pmin}) concentration was 1.7 +/- 0.6 mg/L.

Ciprofloxacin 400mg every 12 hours is the currently recommended dosing schedule for use during CVVHDF therapy in this Hospital. The mean C_{pmax} concentration following 400mg ciprofloxacin twice daily was 5.6 +/- 0.9 mg/L and the mean C_{pmin} concentration following 400mg ciprofloxacin every 12 hours was 2.0 +/- 0.6 mg/L. Davies et al (143) reported a mean trough of 1.27 +/- 0.24 mg/L following multiple dosing with 200mg ciprofloxacin every 8 hours during continuous haemodialysis. MacGowen et al (265) reported a mean C_{pmin} concentration of 0.5 +/- 0.2 mg/L following 200mg ciprofloxacin every 12 hours. Wallis et al (6) observed a mean trough of 0.7 +/- 0.3 mg/L (initial dose) following 200mg every 8 hours and reported accumulation with a mean trough of 1.33 +/- 0.31 mg/L (subsequent doses), while no accumulation was observed by MacGowen et al with 12 hourly dosing. In this study, for patients 1, 3 and 6, there was an increase in trough concentrations with subsequent doses, representing some degree of accumulation (without a change in dosage interval or dose).

6.4 Ciprofloxacin Clearance by CVVHDF

The clearances of ciprofloxacin and creatinine by CVVHDF are presented in Table 6.4.1. The mean clearance of ciprofloxacin by CVVHDF was 2.4 +/- 0.4 L/hr and the clearance of ciprofloxacin by CVVHDF was on average 22% of the TBC. For patients with severe liver impairment (Patients 1, 4, 6 and 7), ciprofloxacin clearance due to CVVHDF accounted for more than a quarter of the Total Body Clearance. In one patient with acute pancreatitis, almost one third of the total ciprofloxacin eliminated was removed by CVVHDF.

Ciprofloxacin Total Body Clearance was reduced in patients with severe liver dysfunction (patients 1, 4, 6 and 7).

Table 6.4.1: Ciprofloxacin and Creatinine Clearance by CVVHDF

Patient Profile	Cl_{CVVHDF} (L/hr)	Cl_{CREAT} (L/hr)	F_{CVVHDF}	Measured effluent fluid rate (L/hr)	Total Body Clearance (L/hr)
1A	2.8	2.9	0.23	4.0	12.1
2C	2.4	2.6	0.16	3.4	14.9
3B	2.7	2.9	0.25	3.9	10.6
4A	2.3	2.3	0.33	2.9	6.9
5A	2.2	2.6	0.19	3.0	11.6
6C	2.1	2.4	0.14	2.9	14.6
7B	2.8	2.9	0.21	4.0	13.4
Mean +/- SD	**2.4 +/- 0.4**	**2.7 +/- 0.3**	**0.22 +/- 0.06**	**3.4 +/- 0.5**	**12.0 +/- 2.8**

Mean ciprofloxacin concentrations in serum and effluent fluid over time are depicted in Figure 6.4.1. The sieving coefficient for ciprofloxacin (S_{cipro}) was 0.70 +/- 0.06. A simple method for estimating drug clearance through the filter, without measuring drug levels, involves using the non-protein bound fraction of ciprofloxacin as an estimate of the sieving coefficient, as it is the unbound fraction that crosses the filter. Hoffken et al and Joos et al have reported fu values for ciprofloxacin of 0.6 and 0.78 respectively. Applying these values to the observed flow rates in this study gives clearance estimates of 2.0 L/hr and 2.7 L/hr, which approximate the measured value of 2.4L/hr. This approach will give a reasonable estimate of ciprofloxacin clearance by the filter that can be considered in conjunction with a deliberation of pharmacokinetic variability in the critically ill patient with organ dysfunction.

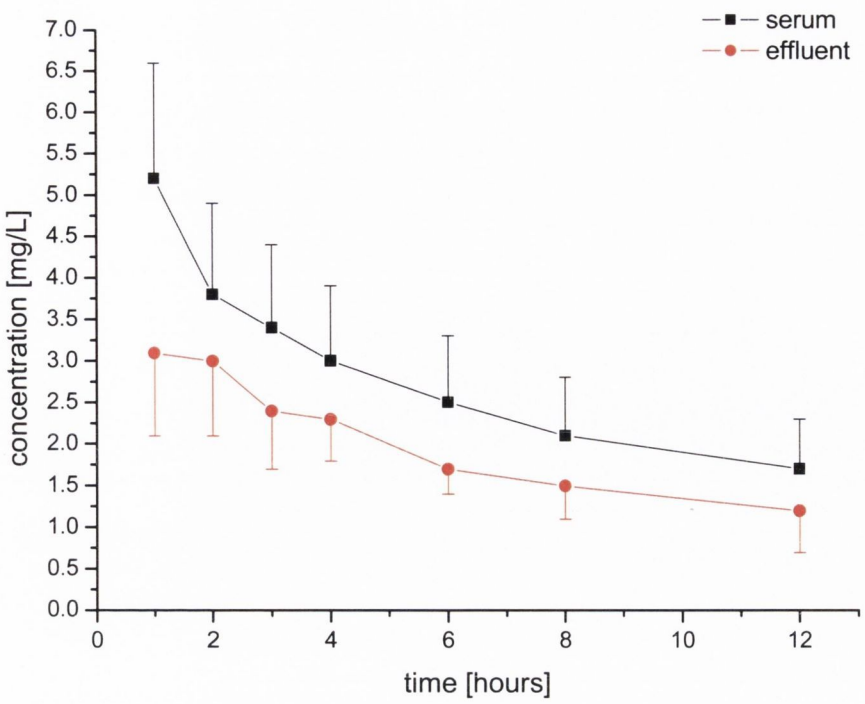


Figure 6.4.1: Concentration-time data for ciprofloxacin in serum and ultrafiltrate during CVVHDF therapy.

The sieving coefficient for creatinine, 0.82 +/- 0.04, was quite similar to that estimated for ciprofloxacin. This finding is clinically important as ciprofloxacin is not routinely assayed in this Hospital and thus it is useful to have a surrogate marker of ciprofloxacin clearance due to CVVHDF, such as creatinine, which is routinely monitored. However, as a marker it somewhat overestimates the clearance for ciprofloxacin due to the slightly higher sieving coefficient for creatinine. The estimate of the clearance of ciprofloxacin due to CVVHDF obtained using this method is 2.6 L/hr, while the actual measured clearance was 2.4 L/hr.

Mean ciprofloxacin concentrations in ultrafiltrate over time are depicted in Figure 6.4.2.

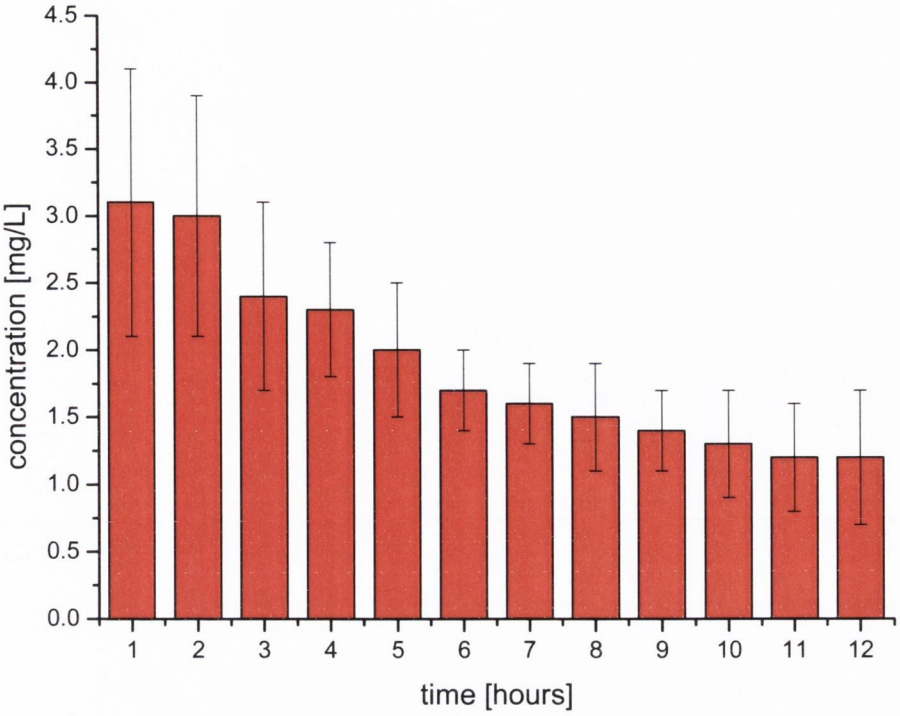


Figure 6.4.2: Mean ciprofloxacin concentrations in ultrafiltrate over time.

Figure 6.4.3 shows that there was little variation in filter performance over time. Ciprofloxacin and creatinine clearances over time were investigated in order to detect any change in filter efficiency over time. No such change was observed and clearance of both creatinine and ciprofloxacin remained relatively constant over the study period. The mean number of filters used per dosage interval was 1.1. The mean duration of use of a filter was 50.6 hours. Filters were changed at the first sign of a problem. In the case of Patient 6, a filter clot occurred during profile C, but the complete serum data set was obtained and the time spent off filter was less than 20 minutes.

Figure 6.4.3 presents Ciprofloxacin clearance and Creatinine clearance data over time.

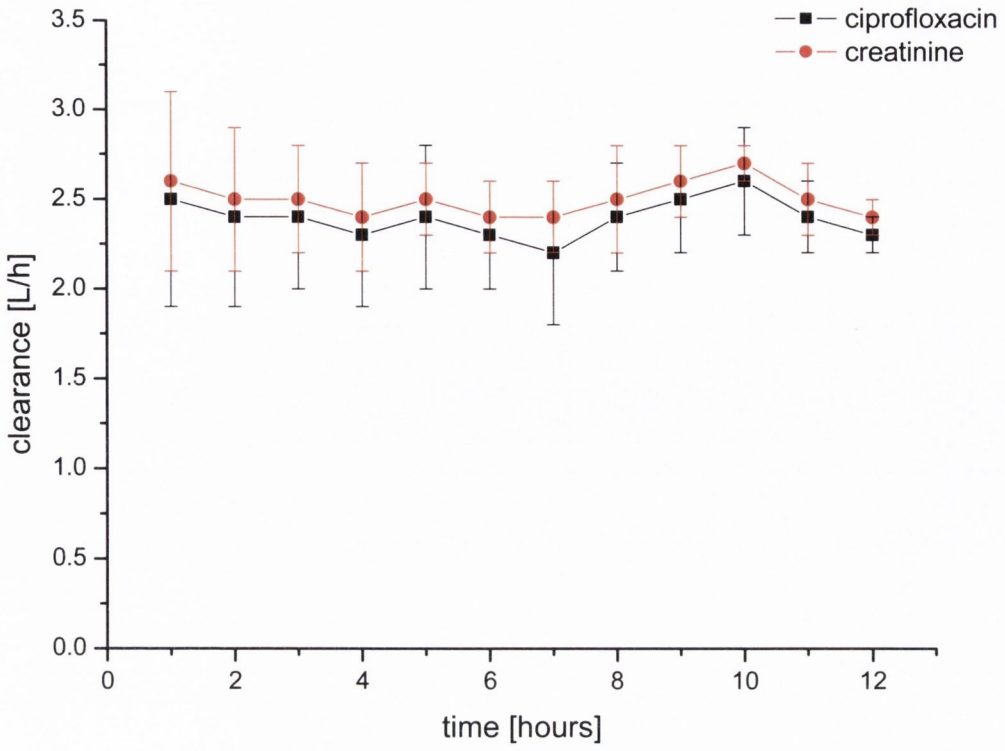


Figure 6.4.3: Ciprofloxacin and Creatinine clearance due to CVVHDF over time.

High C_{pmax}/MIC ratios and the ratio of AUC_{0-24} /MIC have been recommended as good predictors of the likelihood of clinical and microbiological response. The mean area under the serum concentration time curves over a 24 hour period was 59.0 +/- 17.2 mg.hr/L. The lowest AUC_{0-24} was observed in Patient 2 (dose 200mg bd) and the highest AUC_{0-24} was observed in Patient 5 (dose 400mg bd). The lowest and highest C_{pmax} concentrations were also observed in these two patients; a C_{pmax} concentration of 2.6 mg/L was recorded for Patient 2 and a maximum concentration of 7.4 mg/L was measured for Patient 5. A C_{pmax}/MIC ratio of 8 has been suggested as optimal and thus a C_{pmax} concentration of 3.2mg/L would be suitable for pathogens with a MIC of 0.4mg/L. A 400mg twice daily regimen appears to achieve these target concentrations during CVVHDF therapy, while 200mg twice daily appears inadequate.

The mean AUC_{0-24} for patients administered ciprofloxacin 400mg bd was 67.7 +/- 8.7 mg.hr/L. This indicates that a dosing schedule of 400mg twice daily should be adequate for a pathogen with a MIC of up to 0.5mg/L, based on the recommendation that a AUC_{0-24}/MIC > 125 is an indicator of adequate ciprofloxacin dosing.

PK-PD parameters achieved with a ciprofloxacin dosing regimen of 400mg ciprofloxacin every 12 hours, based on an MIC = 0.5mg/L, are given in Table 6.4.2.

Table 6.4.2: Cpmax/MIC ratios for representative MICs for patients treated with 400mg ciprofloxacin every 12 hours during critical illness and CVVHDF therapy.

Patient ID	Cpmax/MIC ratio (MIC = 0.5mg/L)	AUC_{0-24}/MIC ratio (MIC = 0.5mg/L)
1	10.3	143.0
2	10.2	107.6
3	12.8	51.2
4	10.4	149.2
5	14.6	143.6
6	10.0	113.6
7	9.8	59.6

MIC susceptibility testing for pathogens isolated was not performed. Instead representative MICs were considered. Typical MICs for Pseudomonas aeruginosa, Staphylococcus aureus and Escherichia coli are 0.3mg/L, 1mg/L and 0.05mg/L.

On average, the CVVHDF was responsible for clearing a fifth of all ciprofloxacin eliminated. Studies of ciprofloxacin in patients treated with

intermittent haemodialysis and CAPD reported that only small amounts of the drug are removed from serum by these forms of RRT (141). Studies of earlier forms of CRRT observed a haemofilter clearance of only 6% during CAVHDF (270) and 8% in CVVH (274). Thus, CVVHDF clearance of ciprofloxacin exceeds that seen with other forms of RRT. Its relative contribution to TBC is greatest in patients with concurrent hepatic and renal dysfunction, as in these patients, CVVHDF becomes a major route of ciprofloxacin elimination, accounting for up to a third of the TBC.

A ciprofloxacin dosing schedule of 400mg twice daily achieves therapeutic serum concentrations during CVVHDF therapy. Wallis et al (6) used a dosing regimen of 200mg three times daily but concluded that a dosing schedule of 300mg twice daily might be better in terms of achieving higher peak concentrations. Malone et al (272) recommended a once daily ciprofloxacin dose of 400mg once daily during CRRT (CVVH or CVVHDF). The results of this study support the idea of twice daily dosing in order to optimise peak concentrations and to avoid accumulation. A 400mg dose is certainly adequate in terms of achieving optimal C_{pmax} concentrations and a lower dose of 300mg may produce adequate serum concentrations, particularly in patients with multiorgan dysfunction. However, given the general emergence of ciprofloxacin resistance and its increasing use in this Hospital as well as the high tolerability of ciprofloxacin, it may be advisable to maintain this higher ciprofloxacin dosage regimen as the mainstay of therapy, but to consider the possibility of accumulation in patients where more than one elimination route is impaired. Additionally, consideration of the susceptibility of the infective pathogen would allow a more evidence-based approach dosing with individualised PK-PD goals.

Chapter 7. Infective Pathogens and Antimicrobial Usage in ICU Patients treated with CVVHDF: a preliminary investigation of the impact of antimicrobial prescribing on the incidence of multi-drug resistant strains.

7.1 Rationale for investigation

The evaluation of the pharmacokinetics of the antibiotic drugs, amikacin, gentamicin and vancomycin, during CVVHDF therapy indicated much greater clearance of these drugs than had been anticipated, which resulted in sub-therapeutic plasma levels, particularly for the aminoglycosides. In response to this finding and anecdotal reports of poorer antimicrobial efficacy and a higher incidence of resistance among patients treated with CVVHDF, an investigation of pathogens isolated and the incidence of multidrug resistant bacterial strains (MRSA, VRE) in this patient group was undertaken.

7.2 Results

Of the 96 patients treated with CVVHDF during the time period January 2004 to December 2005, 45 were treated empirically. For these patients, it is necessary to balance the need to provide adequate antimicrobial treatment to potentially infected patients with the risk that unnecessary antibiotic treatment carries, such as predisposing to the subsequent emergence of antibiotic-resistant strains. A potential strategy for balancing these two competing issues is the early administration of broad-spectrum antibiotics with rapid adjustment of the antimicrobial regimen on the basis of culture results and the clinical course of the patient. Knowledge of local micororganisms e.g unit specific and their resistance patterns is of great importance for selecting appropriate antimicrobial therapy. Data on the most commonly isolated pathogens among patients treated with CVVHDF in this unit are discussed in

this chapter. 26.6% (12) of these empirically treated patients later tested positive for MRSA during point surveillance screening. The empiric antibiotics used to treat these patients included piperacillin/tazobactam (49%), vancomycin (53%), ciprofloxacin (51%), gentamicin (13%) and meropenem (11%).

The remaining 51 patients were treated on the basis of culture and sensitivity data. For the 96 patients treated with CVVHDF, the most commonly diagnosed infections were pneumonia/lower respiratory tract (LRT) (47%), urinary tract (15%), surgical site (24%) and primary bloodstream infections (20%). (Some patients had more than one suspected infection site). Among the 51 patients with laboratory confirmed infection, the sites of infection were pneumonia/LRT (45%), urinary tract (13%), surgical site (28%), and primary bloodstream (27%). Overall, the most frequently isolated pathogens were Staphylococcus aureus (25.5%), Enterococcus species (23.5%), Coagulase negative staphylococci (21.6%), Pseudomonas aeruginosa (13.7%), Escherichia coli (11.8%) and Klebsiella pneumonia (11.8%). 17 patients developed hospital acquired bloodstream infections (BSI). Staphylococcus aureus, coagulase negative staphylococci and enterococcus faecium were most commonly isolated. 25% of patients with laboratory confirmed infection (n = 13) involved antibiotic-resistant organisms, and 15 (30%) were polymicrobial. The in-hospital death rate was higher for patients with an antimicrobial resistant BSI (46%) compared to those without (22%) ($p<0.001$). The percentage frequencies of bacterial isolates among this patient sample are tabulated in Table 7.1.

Table 7.1: Frequently isolated pathogens in critically ill patients treated with CVVHDF.

Microorganism	**Frequency Percentage (n = 51)**
Staphyloccus aureus, of which **83%** of isolates were methicillin-resistant MRSA	23.5% (12) 19.7% (10)
Coagulase negative staphylococci	21.6% (11)
Enterococcus faecalis	15.7% (8)
Pseudomoas aeruginosa	13.7% (7)
Escherichia coli	11.8% (6)
Klebsiella	11.8% (6)
Actineobacter baumanni	9.8% (5)
Gram negative bacilli	7.8% (4)
Enterococcus faecium	5.9% (3)
Citrobacter freundii	1.9% (1)
Clostridium perfringens	1.9% (1)
Diphtheriods	1.9% (1)
Enterobacter clocae	1.9% (1)

Methicillin resistance among Staphylococcus aureus (S. aureus) isolates was 83%. 96% S.aureus and Enterococcus spp. isolates were susceptible to glycopeptides. One isolate of glycopeptide resistant E. faecium and one glycopeptide resistant E. faecalis isolate were identified. In both cases, patients had been hospital in-patients for durations of 13 and 19 days respectively. The

first patient had previously received flucloxacillin and benzylpenicillin for cellulitis and vancomycin NG for C. difficile infection prior to admission to ICU. The second patient received co-amoxiclav and ciprofloxacin on the ward for an acute infective exacerbation of COPD. Staphylococcus aureus isolates in two patients were resistant to linezolid. Both patients had previous antibiotic exposure and prolonged hospital stay (12, 45 days). There was a significant increase in linezolid usage in the time period January 2004-Decmeber 2005 (23.1%), compared to that recorded for the time period January-December 2003 (12.2%, Chp3). This increased usage of linezolid may be an indicator of the failure to optimise the use of vancomycin with the consequent observed emergence of vancomycin-resistant enterococci (VRE).

Table 7.2: Incidence of multi-drug resistant S.aureus and Enterococcus spp. in ICU patients treated with CVVHDF

Pathogen	**Percentage frequency prevalence of pathogen among ICU patients treated with CVVHDF in the time period January 2004 - December 2005 (n=96)**
MRSA	22.9
VRE	3.1
Linezolid-resistant S. aureus	2.1

Overall, there was an increase in the incidence of MRSA in the patient sample in 2004 to 2005 (22.9%), compared to the sample examined in 2003 (12.8%) (Chp 3). There was one incidence of ciprofloxacin-resistant Klebsiella pneumonia in a patient previously treated with oral ciprofloxacin, gentamicin and vancomycin. There were two further patients with infection due to ciprofloxacin-reistant pseudomonas aeruginosa whom were previously treated with gentamicin and vancomycin. Pseudomonas aeruginosa isolates (n=7)

were most frequently sensitive to piperacillin/tazobactam (86%), meropenem (86%) and amikacin (71%).

In 22.2% of patients treated with an aminoglycoside (amikacin/gentamicin) for documented infection during CVVHDF therapy, aminoglycoside resistance emerged during therapy (mean no. days after initiating therapy = 4.2). Although, the sample size is small this is suggestive that the suboptimal dosing of aminoglycosides during CVVHDF, described in Chapter 5, may have contributed to the emergence of drug resistant strains. 44.4% of patients treated with gentamicin during CVVHDF were MRSA positive and received concurrent gram-positive antimicrobial cover (vancomycin (40.7%), linezolid (3.9%)) therapy.

In 33.9% of patients treated with ciprofloxacin for gram-negative infection during CVVHDF, staphyloccus aureus isolates were resistant to methicillin. Gentamicin dosing schedules and pharmacokinetic profiles in the patients, where resistance of Acinetobacter baumannii and E. coli subsequently developed during therapy, were analysed. The mean duration of gentamicin therapy was 7 days and the mean dose was 290mg once daily. The range of C_{pmax} concentration achieved was 4.9 – 11.4 mg/L. As C_{pmax} concentrations are indicators of efficacy for the aminoglycosides and the target range of C_{pmax} concentrations is 10-25mg/L, these subtherapeutic concentrations may have had a role in the development of gentamicin-resistant strains.

The most commonly prescribed antimicrobial agents, among this patient sample, were metronidazole (52%), ciprofloxacin (59%), vancomycin (68%) and piperacillin/tazobactam (47%). This is similar to the antimicriobial usage reported during CVVHDF in the audit described in Chapter 3, where data

generated during an earlier time period (January – December 2003) was analysed.

7.3 Discussion:

The prevalence of multidrug resistant strains in ICU patients treated with CVVHDF is increasing. The emergence of VRE in a small number of patients may relate to failure to rationalise vancomycin dosing resulting in therapy failure particularly in the context of changing local ecology, reflected by an increased usage of linezolid. This has been acknowledged by the Microbiology team and ICU usage of linezolid was reviewed in December 2005 and decreased for patients treated with CVVHDF in the time period January to July 2006 from that recorded in July to December 2005. Additionally, low and borderline vancomycin trough serum concentrations may have been a contributing factor to the emergence of resistance. As described in Chapter 4, the most commonly prescribed vancomycin dosage regimen during CVVHDF was 1g every 24 hours. The range of trough concentrations achieved by this dosing schedule was 3.7 – 12.4mg/L. Trough concentrations at the lower end of this range, particularly concentrations < 5mg/L, will present an increased risk of therapy failure. In response to the increased incidence of MRSA among these patients necessitating greater use of glycopeptides, and the occurrence of a number of cases of VRE, new target trough concentrations have been introduced for ICU patients treated with CVVHDF (10-15mg/L rather than 5-12mg/L). This is consistent with literature reports that higher vancomycin serum concentrations are desirable in critically ill patients. The optimal approach to achieving these higher target serum concentrations is to adjust the dosage interval on the basis of estimates of the individual patient's elimination parameters. As discussed in Chapter 4,

a dosage interval of 18 hours may be preferable to the previously prescribed 24 hours, as it is closer to the estimated half-life in ICU patients treated with CVVHDF.

The development of aminoglycoside resistance during treatment with amikacin and gentamicin in patients receiving CVVHDF is a concern. As it is likely that the emergence of such resistance related to the inadequate serum concentrations associated with the dosing practices described in Chapter 5, the new higher individualised doses should act to address this problem.

The importance of aggressively treating multi-drug resistant bacterial strains and avoiding its development is highlighted by the high death rates observed in patients with multidrug resistant BSI. Previous studies have identified an important association between the administration of inadequate antimicrobial treatment of BSI and hospital mortality (275). Leibovici and coworkers (275) found that the hospital mortality rate was significantly lower for patients with BSI who received adequate antimicrobial treatment compared with inadequate treatment. Similarly, Weinstein et al (276) showed that patients who received adequate antimicrobial treatment throughout the course of BSI had the lowest mortality.

The emergence of resistance to ciprofloxacin is an issue of international concern. Although, usage of ciprofloxacin has increased in the Hospital generally in the past two years, its high level of usage has remained relatively constant among ICU patients treated with CVVHDF. Presently, the dosing schedule generally used for patients during CVVHDF (400mg every 12 hours) in this ICU represents a higher daily dose than has been reported in the literature (600mg by Wallis et al (6), 400mg by Malone et al (272)). This dosing schedule achieves ciprofloxacin serum concentrations considered

adequate in terms of clinical response and avoiding the emergence of resistance.

This review of resistance data and antimicrobial prescribing for patients treated with CVVHDF examined antibiotic usage in terms of the number of patients treated with a particular antibiotic, rather than using defined daily doses (DDDs) for the ICU as a whole. Although, this approach is more time-consuming, the use of DDDs for a patient population such as critically ill patients treated with CVVHDF is misleading. This is because of the need for individualised dosage adjustment of many antimicrobial drugs during critical illness and treatment with CVVHDF. This data suggests that it is not only the correct choice of antimicrobial agent but also the use of sufficiently high doses that is important in influencing the level of resistance among patients treated with CVVHDF. The pattern of antibiotic usage during the time period January 2003 to July 2006 has remained relatively constant, with the exception of increased usage of linezolid in the time period June to December 2005. However, the incidence of drug resistance, in particular MRSA, has increased with the emergence of VRE. There was a similar incidence of MRSA among patients treated empirically as those treated with a particular agent on the basis of sensitivity data. Sensitivity data and culture results were only used to support the choice of agent rather than to select the optimum dose. Thus, this data suggests that adequate dosing is as important a factor as choosing the 'right' antibiotic for infection in ICU patients receiving CVVHDF. The general recommendations culminating from this data is that dosing of aminoglycosides during CVVHDF should focus on achieving optimal C_{pmax}/MIC ratios, as outlined in Chapter 5, higher vancomycin trough concentrations should be targeted with appropriate dosage interval adjustment

and linezolid usage should be restricted. In this study it has been observed that when a specific antibiotic is recommended for a particular patient by the microbiology team or an ICU consultant, little advice is provided on dosage to the prescribing NCHD. The importance of an appropriate individualised dose should be emphasised and where possible the dose selected should be on the basis of sensitivity data (e.g. MIC) and where possible estimates of patient's individualised pharmacokinetic parameters i.e. PK-PD goals.

Chapter 8. General Discussion

8.1 Patient Demographics and Clinical Characteristics

Drug pharmacokinetics during CVVHDF therapy involves a complex interchange between drug factors, patient factors and CVVHDF conditions. Drug pharmacokinetics during CVVHDF were considered in 25 patients retrospectively and 32 patients prospectively. The mean age of patients treated with vancomycin was 60.5 +/- 14.3 years (range: 30-85 years). Among the retrospective and prospective patient samples, the range of patient ages was 40 -75 years for amikacin and 43 -75 years for gentamicin. Patients treated with ciprofloxacin ranged from 28 to 77 years. Although dosage adjustment of many antimicrobial drugs, including vancomycin, aminoglycosides and ciprofloxacin, is often recommended for elderly patients, there was no statistically significant dose-age relationship for any of the drugs analysed in this study ($p>0.05$). Dosage reduction of these drugs is generally suggested for elderly patients primarily on the basis of declining renal function. However, as all patients had ARF, dosing trends due to age-related renal dysfunction are likely to have been obscured. A higher proportion of patients treated with CVVHDF and the relevant antimicrobial drugs were male (0.6). This may reflect reports of a higher incidence of sepsis among males, for example; a large study of the epidemiology of sepsis in the US from 1979 to 2000 reported a higher mean annual relative risk for sepsis for men compared to women (277). No statistically significant differences in dose, dosage frequency or drug pharmacokinetics (TBC, Vd) among male and female patients were observed ($p>0.05$). Patients presented with a diverse range of comorbidities, including liver disease, respiratory disorders, diabetes, and CVD. Of the 32 patients recruited for the prospective study, eight patients were admitted to the ICU post-surgery. The most common surgical procedures were for colonic/intestinal/bowel obstruction

and AAA repair. 38% of patients recruited had concurrent hepatic and renal dysfunction (n=12). All patients had severe renal impairment. Five patients had acute on chronic renal impairment. The study group was thus representative of a wide range of ICU admissions requiring antimicrobial therapy and renal support.

8.2 Analysis of Clinical Outcomes

For patients treated with vancomycin, amikacin, gentamicin and ciprofloxacin, the mean SOFA and APACHE II scores were comparable (Table 8.1). Survival rates among patients treated with amikacin and gentamicin in the prospective study were higher than among the patient sample analysed retrospectively. Survival rates among patients treated with vancomycin were slightly higher among the prospective sample compared to the retrospective sample. More than two thirds of patients treated with ciprofloxacin and CVVHDF therapy concurrently survived treatment.

APACHE II scores and SOFA scores together with in-hospital deaths for the retrospective and prospective patient samples are compared in Table 8.1.

Table 8.1: Comparison of APACHE II and SOFA scores for patients prescribed amikacin, gentamicin, vancomycin and ciprofloxacin during CVVHDF

Patient Sample	Mean APACHE II score	Mean SOFA score	Number of in-hospital Deaths (% frequency)
Vancomycin Retrospective n=16	23.3 +/- 6.9	8.38 +/-3.2	8 (50%)
Vancomycin Prospective n=13	25.5 +/- 4.0	8.15 +/- 2.4	5 (38%)
Amikacin Retrospective n=5	22.8 +/- 4.0	8.2 +/- 2.0	5 (100%)
Amikacin Prospective n= 5	26.6 +/- 7.8	5.4 +/- 1.1	2 (40%)
Gentamicin Retrospective n=4	28.3 +/- 2.8	6.4 +/- 1.4	3 (75%)
Gentamicin Prospective n=7	29.1 +/- 6.8	6.9 +/- 1.8	2 (29%)
Ciprofloxacin Prospective n= 7	27.4 +/- 1.7	8.6 +/- 2.4	2 (29%)

8.3 Retrospective versus Prospective Samples: Dose Comparison

Aminoglycoside doses prescribed in the prospective study were higher than those prescribed in the retrospective study. There was a 128% increase in the mean amikacin dose and a 26% increase in the mean gentamicin dose, observed retrospectively versus prescribed prospectively. The mean amikacin dose administered among the retrospective sample was 552 +/- 177mg and was significantly lower than the mean dose prescribed in the prospective study; 1258 +/- 396 mg. The mean amikacin C_{pmax} concentration among the retrospective sample was 19.6 +/- 1.6 mg/L, compared to a higher C_{pmax} of 43.1 +/- 15.1 mg/L, achieved in the prospective study. The mean dosage intervals observed retrospectively and prescribed prospectively were 23.5 +/- 1.6 hours

and 25.5 +/- 8.5 hours respectively. For gentamicin, the mean doses in the retrospective and prospective studies were 263 +/- 58 mg and 331 +/- 41 mg respectively. The respective dosage intervals were 25.6 +/- 2.9 hours and 24.4 +/- 1.1 hours. C_{pmax} concentrations observed retrospectively and achieved prospectively were 9.1 +/- 3.3 mg/L and 12.7 +/- 2.34 mg/L respectively. This data is summarised in Table 8.2:

Table 8.2: Comparison of dosing schedules and serum concentrations in the retrospective and prospective studies

Patient sample	Dose (mean +/- sd) mg	Dosage interval (mean +/- sd) Hours	Cpmax conc. (mean +/- sd) (mg/L)	Cpmin conc. (mean +/- sd) (mg/L)
Amikacin (Retrospective)	552 +/- 176	23.5 +/- 1.6	19.6 +/- 1.6	2.7 +/- 1.5
Amikacin (Prospective)	1258 +/- 396	25.5 +/- 8.5	43.1 +/- 15.1	3.7 +/- 1.7
Gentamicin (Retrospective)	263 +/- 58	25.6 +/- 2.9	9.1 +/- 3.3	1.1 +/- 0.3
Gentamicin (Prospective)	331 +/- 41	24.4 +/- 1.1	12.7 +/- 2.3	1.3 +/- 0.3

The mean vancomycin trough concentration observed among the retrospective sample treated with CVVHDF was similar to that achieved during the prospective study; 10.2 +/- 4.2 mg/L, compared to 11.3mg/L.

8.4 Antimicrobial Drug Pharmacokinetics during CVVHDF

Drugs that are primarily renally eliminated, with a molecular weight of less than 5000 Da, low protein binding and a small Vd are likely to be significantly cleared by CVVHDF. Glycopeptides and aminoglycosides are examples of antibiotics that meet these criteria. In renal impairment, dosage reduction of these drugs is recommended but subtherapeutic dosage of drugs can be even more danagerous than overdosage, especially for anti-infective therapy in critically ill patients.

8.4.1 Vancomycin Pharmacokinetics during CVVHDF

Vancomycin is the second most frequently used antibiotic during CVVHDF therapy at AMNCH. Due to this high usage, its potential clearance by CVVHDF and its narrow therapeutic index, a retrospective analysis of vancomycin serum concentrations obtained during treatment with CVVHDF was undertaken. This retrospective study sought to investigate whether routine TDM data could be used to determine meaningful individual patient estimates of k, Vd, ($t_{1/2}$, Cl) for critically ill patients treated with CVVHDF.

Of the available TDM data, fifty percent met the criteria required for inclusion in the analysis. Estimates of pharmacokinetic parameters were obtained that agreed closely with those reported in a small prospective study (145) (n=3 patients) of vancomycin pharmacokinetics during CVVHDF and a further prospective study of vancomycin during CVVH (142) (n=2). Estimates of elimination parameters for vancomycin obtained in the retrospective study suggested that elimination rate constants during CVVHDF were approximately 8-10 times those seen in anuric nondialysed patients and about half that seen in patients with normal renal function. The mean half-life during CVVHDF was 16.8 +/- 2.5 hours and the interpatient coefficient of variation (CV) was quite low (16.9%). This half-life value was slightly longer than that reported in a literature study of vancomycin

pharmacokinetics in three patients treated with CVVHDF. Santre et al (145) reported a mean half-life of 13.9 hours for these three patients. Booreboom et al (142) reported a mean half-life of 17.9 hours for two patients treated with CVVH. Matzke et al (116) evaluated the effect of intermittent hemofiltration on vancomycin disposition in five patients and reported that the half-life was reduced to 4.1 hours during haemofiltration from 136.0 hours in the interdialytic period. In this study, a higher level of variability was observed for Vd estimates, than for k, and in general values were higher than those reported for subjects without renal dysfunction or critical illness. The mean value of Vd was 57.5 +/- 12.8 L and the interpatient CV was 22.3%.

The TBC (2.45L/hr) was 1.3 - 6.5 times that reported during other forms of CRRT. It agreed well with the TBC value (2.33L/hr) for vancomycin reported by Santre et al (145)(n=3). The value for vancomycin TBC during CVVH reported by Boereboom et al (116) was slightly lower; with a mean value of 1.95 L/hr. Macias et al (117) had also reported a lower TBC in an earlier study of CVVH (1.7 +/- 0.4 L/hr). The combination of convective and diffusive forces employed in CVVHDF results in more efficient vancomycin clearance.

The mean creatinine clearance prior to commencing CVVHDF was 0.3L/hr. If creatinine clearance is used as an approximate of vancomycin clearance, CVVHDF results in an estimated 8-fold increase in the TBC of vancomycin.

A prospective study of vancomycin pharmacokinetics during CVVHDF therapy was subsequently designed. The prospective study design facilitated the collection of multiple serum samples in a dosage interval and effluent fluid collection. In the retrospective study, equations based on a one-compartment model using the SZM were used to obtain estimates of k, Vd, ($t_{1/2}$, Cl). The availability of multiple serum samples in a dosage interval in the prospective study allowed both a 1-

compartment model and a 2-compartment model to be fitted to the serum concentration-time data. This meant that estimates of pharmacokinetic parameters obtained using both models could be compared. Thus, the prospective study allowed an assessment of the validity of using two serum concentrations in a dosage interval on the basis of a one-compartment model to determine individual patient pharmacokinetic parameters for vancomycin during CVVHDF. Although, a 2-compartment model resulted in a better fit, estimates of pharmacokinetic parameters obtained using a 1- or 2- compartment model were not significantly different ($p>0.05$, $p = 0.31$).

The prospective study also involved collection of effluent fluid data. This meant that clearance due to CVVHDF could be examined as a proportion of TBC. Thus, it was found that on average 82 +/- 15 % of vancomycin TBC was due to CVVHDF. The mean clearance of vancomycin by CVVHDF was 2.1 +/- 0.3 L/hr, with a mean effluent fluid flow rate of 3.1 +/- 0.4 L/hr. As the effluent flow rate increased, an increase in Cl_{CVVHDF} was observed (Figure 8.2, Section 8.7). In a recent study, DelDot et al (147) reported a similar value of 1.8 +/- 0.4 L/hr for vancomycin clearance due to CVVHDF, under similar technical conditions. In our study, there was some discrepancy between the actual fluid flow rates observed (3.1 +/- 0.4 L/hr) and those prescribed or recorded in the nursing notes (3.3 +/- 0.5 L/hr). Santre et al (145) reported a far smaller contribution to TBC by CVVHDF (5-15%), when much lower effluent fluid flow rates were achieved. Lau and John (278) evaluated vancomycin clearance during CAVH with an Amicon D-20 filter in a 15 month old child with ARF and reported that 70% of the TBC of vancomycin was due to CAVH. Dupuis et al (279) reported an effective clearance of 9L/day by CAVH in a 48 year old man, using an Amicon D-10 filter.

Creatinine clearance by CVVHDF was estimated as 2.25 +/- 0.26 L/hr. This corresponds to the renal function of a nondialysed patient with a moderate degree of renal function. No change in CVVHDF performance over time was detected. The mean sieving coefficient for vancomycin was 0.71 +/- and was consistent with that previously reported in the literature (142,145).

Among the prospective study patient sample, the mean elimination rate constant during CVVHDF was 0.06 +/- 0.02 hr^{-1}. The mean half-life was 14.0 +/- 4.6 hours and this is similar to the half-life of 13.9 hours reported by Santre et al (145) and the value of 16.6 +/- 8.7 hours observed by DelDot et al (147) in a more recent study. DelDot et al used a dosing regimen of 750mg/12 hours, which resulted in accumulation. This observation is explained by the estimated half-life which exceeds the dosage interval. Our data demonstrates that the use of higher doses with extension of the dosage interval avoids accumulation while maintaining adequate serum concentrations during CVVHDF therapy.

The Vd was at the higher end of the range observed in patients with normal renal function. The Vd measured in this study is consistent with that previously reported by Santre (145) and DelDot (147) and with other studies investigating the removal of vancomycin using different filter types and CRRT conditions (141-143).

In conclusion, vancomycin is effectively cleared by CVVHDF under the conditions of use described in this study. The clearance is greater than for other less efficient forms of CRRT. A dose of 1g every 24 hours is adequate for most patients treated with CVVHDF, where the MIC of the susceptible bacteria is 1-2mg/L and a trough/MIC ratio of 5 is targeted. For patients with more resistant strains or a higher Vd, higher doses of up to 1.5g every 24 hours may be necessary to maintain target serum concentrations. An alternative and preferred approach given the pharmacodynamic properties of vancomycin is to shorten the dosage

interval in patients where it is necessary to maintain higher serum concentrations. An estimate of the elimination half-life for an individual patient will help to identify an appropriate dosage interval. For example, a dosage interval of 18 hours has been considered for use during CVVHDF in this unit, as dosing at intervals close to the estimated half-life will reduce the likelihood of accumulation, while maintaining adequate serum concentrations.

In response to literature reports and the incidence of drug resistant pathogens identified in this study, target vancomycin trough concentrations for ICU patients in this Hospital have been revised. Achieving these higher serum concentrations will required individualised adjustment of dosage intervals on the basis of estimated elimination parameters.

8.4.2 Aminoglycoside Pharmacokinetics during CVVHDF

Currently, there is no published data on amikacin or gentamicin pharmacokinetics during CVVHDF. The audit of drug use during CVVHDF (Chapter 3) indicated that these drugs are sometimes used in patients treated with CVVHDF. Determining the optimal dose for these drugs can be difficult, due to their narrow therapeutic windows and the absence of literature data on their behaviour during CVVHDF. Using a similar approach to that adopted for vancomycin, a retrospective analysis of amikacin and gentamicin serum concentration data collected during TDM for patients treated with CVVHDF over a 12 month period was carried out. Sixty-nine percent of the available TDM data met the criteria required for pharmacokinetic analysis. The results of this analysis indicated that clearance of these drugs during CVVHDF therapy was greater than anticipated and had resulted in subtherapeutic dosing. For amikacin, 100% of C_{pmax} concentrations were below the minimum target concentration (40mg/L) and 64% of C_{pmax}

concentrations were below the target range for gentamicin (10-20mg/L). Estimates of k, Vd ($t_{1/2}$, Cl) were calculated for amikacin and gentamicin. The mean amikacin half-life during CVVHDF therapy was 8.8 +/- 1.2 hours. Treatment with CVVHDF therapy resulted in a more than 3-fold reduction in the elimination half-life. As for vancomycin, the elimination half-life during CVVHDF was approximately twice that reported for patients with normal renal function. A study of amikacin pharmacokinetics during intermittent haemofiltration had reported a half-life of 3.5 hours during the haemofiltration period (222). However, there were dissimilarities in the patient mix, in addition to the different modality of RRT employed; patients were stable with ESRF rather than critically ill with ARF, which makes comparison of our results difficult.

The observed Vd, 32 +/- 8 L, was higher than for patients without renal dysfunction or critical illness. This is consistent with literature reports of an increased Vd for the aminoglycosides in critically ill patients (214,219). The mean amikacin TBC was 2.7 +/- 0.5 L/hr.

For gentamicin, the mean elimination half-life was slightly lower but very similar to that determined for amikacin (8.6 +/- 1.5 hours vs. 8.8 +/- 1.2 hours). The mean gentamicin TBC was almost the same as for amikacin (2.8 L/hr vs 2.7 L/hr). The Vd was 34 +/- 8 L/hr, which was again similar to that estimated for amikacin.

Prior to the commencement of the prospective pharmacokinetic study and clinical evaluation of these drugs during CVVHDF, general recommendations on the dosing of these drugs during CVVHDF were introduced in response to the findings of the retrospective analysis. It was recommended that a loading dose, similar to those given to patients with normal renal function should be administered and that further dosage adjustment should be made on the basis of serum drug concentrations. Additionally, it was advised that where dosage adjustment was

necessary that the optimal approach was to extend the dosage interval, in order to increase the likelihood of achieving target C_{pmax}/MIC goals and to reduce the risk of accumulation. Previously, the primary method of dosage adjustment had been to reduce the dose on the basis of renal impairment, thus resulting in low C_{pmax} concentrations and increasing the risk of therapy failure. The subtherapeutic dosing of aminoglycosides identified in the retrospective analysis resulted from a number of factors. Among these factors was the absence of literature data on aminoglycoside pharmacokinetics during CVVHDF, which meant that doses had to be selected without a definite evidence-base. Secondly, the TBC observed during CVVHDF was much greater than had been reported for less efficient forms of CRRT. This meant that application of the results of these studies led to underdosing of patients treated with CVVHDF. Finally, an elevated Vd was observed for both amikacin and gentamicin, in comparison to that reported for patients with normal renal function or in stable patients with renal dysfunction; and this contributed to the inadequacy of doses in terms of achieving target serum concentrations.

During the prospective study, estimates of pharmacokinetic parameters were used to determine appropriate dosage regimens and to achieve serum concentrations within the target range. The application of the SZM to two serum concentrations obtained in a dosage interval yielded estimates of pharmacokinetic parameters for amikacin and gentamicin, similar to those obtained by fitting a one-compartment model to multiple serum concentrations monitored in a single dosage interval. Furthermore, estimates of pharmacokinetic parameters obtained by applying a one-compartment model did not differ significantly from those derived using a two-compartment model in the same patients.

Patient factors, such as alterations in Vd, resulted in changes in drug serum concentrations and dosing requirements. In general, for the aminoglycosides, the Vd was higher than in patients with normal renal function and there was a trend of a decreasing Vd over time during treatment with CVVHDF. This can be explained by changes in the patient's fluid status; at the start of CVVHDF therapy, patients tend to be fluid overloaded and with CVVHDF removal of excess fluid results in a reduction in the observed Vd as aminoglycosides are distributed in the ECF. Sepsis and neutropenic sepsis have been associated with an increased Vd for the aminoglycosides (215, 218). All seven of the patients treated with gentamicin in the prospective study had sepsis and four of the five patients treated with amikacin had sepsis. One of the patients treated with amikacin had neutropenic sepsis and a particularly high clearance was observed in this patient. For vancomycin, the Vd in patients with oedema was significantly higher than those without oedema.

The mean clearance of Gentamicin due to CVVHDF was 2.3 +/- 0.3 L/hr. This is 82% of the total body clearance of Gentamicin. The mean clearance of amikacin by CVVHDF was 2.9 +/- 0.4 L/hr, which was 91% of the total body clearance. The sieving coefficient for amikacin was 0.83 +/- 0.05, while the sieving coefficient for gentamicin was 0.85 +/- 0.05. As the sieving coefficients for both drugs were similar, and clearance by CVVHDF is given by the product of the sieving coefficient and the flow rate (Cl = S.C. X Q), this suggests that the higher effluent flow rates used in the treatment of patients receiving amikacin, were primarily responsible for the greater clearances of amikacin in this study. The mean effluent flow rate achieved among the patient sample concurrently treated with Gentamicin and CVVHDF was 2.71 L/hr, while the mean flow rate achieved during amikacin therapy was 3.53 L/hr.

8.4.3 Management of Aminoglycoside and Vancomycin therapy during CVVHDF

Vancomycin and the Aminoglycosides share common characteristics in that they are primarily renally eliminated, exhibit low protein binding and have narrow therapeutic windows. This study demonstrates that the pharmacokinetics of these water-soluble, renally-eliminated drugs are significantly altered in critically ill patients by treatment with CVVDHF. In general, CVVHDF effectively clears these drugs. For both groups of drugs, the elimination rate constant is approximately half that observed in patients with normal renal function and is significantly greater than reported for nondialysed anuric patients or those treated with less efficient forms of RRT.

However, vancomycin and the aminoglycosides differ significantly in terms of their pharmacodynamic properties. These differences are reflected in their appropriate PK-PD goals. While maintaining serum concentrations above the MIC of susceptible bacteria should be the goal of vancomycin therapy, for the aminoglycosides, it is important to achieve a high C_{pmax}/MIC ratio. Thus, for vancomycin, trough concentrations are indicators of the likelihood of therapeutic efficacy, while for the aminoglycosides high C_{pmax} concentrations are better predictors of therapeutic response.

These pharmacokinetic and pharmacodynamic factors must be considered when designing optimal dosing strategies for individual patients during CVVHDF. The initial loading dose should not be adjusted for renal impairment. This is particularly important for the aminoglycosides, where high C_{pmax} concentrations early in therapy increase the likelihood of therapeutic response and reduce the risk of adaptive tolerance. Instead, the usual loading dose should be administered and serum concentrations should be used to determine the optimal dosage interval.

For vancomycin, having obtained estimates of k, Vd ($t_{1/2}$, Cl), the dosage interval should be adjusted so as to maintain C_{pmin} concentrations above a target concentration, ideally based on the MIC of the etiologic agent. Dosing at intervals of the estimated half-life will avoid accumulation while maintaining therapeutic trough concentrations.

Dosage adjustment for the aminoglycosides should focus on achieving a desired C_{pmax} concentration, while extending the dosage interval to avoid accumulation. Aminoglycoside dosing should be individualised throughout CVVHDF therapy due to the potential for changes in patient factors and CVVHDF conditions resulting in altered pharmacokinetics. A changing Vd can be anticipated and estimates of Vd should guide dosing. Additionally, changes in CVVHDF conditions will impact on drug elimination. If there is an extended interruption to CVVHDF therapy, the drug half-life will be extended dramatically and extension of the dosage interval will be required. We have adopted the practice of measuring a drug serum concentration as soon as CVVHDF therapy is recommenced and using a rearrangement of equation 1.2.6.7, we predict when serum concentrations should have fallen to the target trough concentration range. If there is a change in ultrafiltrate/dialysate flow rates, this will also alter clearance due to CVVHDF. The use of sieving coefficients and the 'new' flow rates will allow an estimation of the change in CVVHDF clearance and the likely impact on the elimination half-life of the drug.

8.4.4 TDM recommendations

Given the degree of pharmacokinetic variability observed for the aminoglycosides and vancomycin during CVVHDF therapy, at least two timed drug serum concentrations should be monitored in a dosage interval. As these drugs have a detectable distribution phase, the 'peak' concentration should be taken at a time point where distribution is likely to be complete. For vancomycin, extension of the peak sampling time to two hours after the infusion is complete has been recommended. For the aminoglycosides, it is advisable to infuse the drug over 60 minutes rather than 30 minutes, to obscure the distribution phase. Where a 'random' concentration and a trough concentration are measured in the same dosage interval and exact sampling times are recorded, these two serum concentrations can be used to obtain an estimate of k and $t_{1/2}$. Critical details such as the time at which the infusion was started and complete, the exact time of serum sampling, the dose and dosage interval must be accurately documented for appropriate interpretation of levels and to allow estimation of individual patient pharmacokinetic parameters. Among the available vancomycin TDM data considered for inclusion in the retrospective analysis, only 50% of this data met the criteria required for pharmacokinetic analysis. In response to this finding, education of ICU nurses and NCHDs on improved TDM procedures was initiated. The importance of accurately recording defined 'critical data' and in particular exact infusion and serum sampling times was emphasised. The DCF designed for recording this data for the prospective study was piloted and feedback was sought from a multidisciplinary panel as part of this induction process. As a result of this review of the TDM process, there was a significant improvement in the quality of data collated and 98% of the serum concentration data collected for the aminoglycosides and vancomycin during the prospective study was amenable to

pharmacokinetic analysis. This demonstrates that intensive staff induction with the necessary supportive documentation can improve the quality of TDM procedures. It is acknowledged that such a review process is particularly likely to succeed in a controlled environment such as ICU.

As part of the review of TDM procedures, the target concentration ranges in use for vancomycin and the aminoglycosides were considered. Additionally, the requirement for different approaches to the therapeutic management of these drugs, which reflect their varying pharmacodynamic properties, was communicated to medical staff.

Common target concentration ranges are used for all patients in the Hospital. PK-PD goals were not set for individual patients and in this sense therapy was not goal-directed. This approach is not ideal as there should be a risk-benefit analysis for each patient. If the need for therapy is low, then the risks of treatment should be low. However, if previous antimicrobial therapy has failed and therapeutic efficacy is essential in terms of patient survival, then a higher risk of toxicity can be tolerated. For the aminoglycosides and ciprofloxacin, where antimicrobial efficacy is concentration-dependent and relates to the ratio of C_{pmax} to MIC, then PK-PD goals should be set on the basis of MIC data. In this way, aggressive therapy can be instituted only where it is indicated and lower doses can be used to treat patients with less resistant strains, where lower serum concentrations are likely to be adequate. Throughout the prospective study, wherever MIC data was available, this was used to identify appropriate PK-PD goals, for example as discussed in relation to gentamicin (Chapter 5.2).

In terms of antimicrobial prescribing in this ICU, the emphasis appears to be on selecting the 'right' antibiotic rather than optimising the dose. Failure to respond to an antibiotic was more usually interpreted as resistance rather than the use of a

suboptimal dose. While suboptimal dosing appears to be leading to the emergence of resistance, resistance was often not the primary reason for therapy failure.

8.5 Ciprofloxacin pharmacokinetics during CVVHDF

For ciprofloxacin, there is more than one significant route of elimination. Although the renal route it the primary route of eliminiation, ciprofloxacin is also cleared via the hepatic and transintestinal route. Ciprofloxacin also has a higher Vd than the aminoglycosides or vancomycin. In this study, greater variability in the elimination half-life was observed for ciprofloxacin (CV = 42.7%), in comparison to vancomcyin and the aminoglycosides. Specifically defining the elimination rate constant for this population may be difficult. The range in half-lives was 4.7 -17.2 hours. Hepatic dysfunction influenced the elimination half-life; the longest elimination half-life was observed in a patient with acute pancreatitis. CVVHDF accounted for 33.3% of the TBC of ciprofloxacin in this patient.

In this study, CVVHDF accounted for on average 22% of the TBC. This is higher than the 15% contribution to TBC reported by Malone et al (272) but close to the 21% observed by Wallis et al (6). Generally, the contribution of CVVHDF to TBC was greater in patients with concurrent hepatic and renal impairment.

The sieving coefficient for ciprofloxacin was 0.70 +/- 0.06. This is similar to the sieving coefficient values reported by Wallis et al (6) using the same filter and similar conditions (0.70 +/- 0.13) and slightly lower than that observed by Davies et al (143) using different conditions but the same filter (0.77 +/- 0.17). Malone et al (272) reported a range of sieving coefficient values for ciprofloxacin, 0.53 to 0.69, estimated for five patients treated with CVVHDF using the same filter but lower effluent flow rates (UF rate range = 0.8 L/hr – 1.4 L/hr). The mean effluent flow rate achieved during CVVHDF therapy in this study was 3.4 +/- 0.5L/hr,

while the reported flow rate in the study by Wallis et al (6) was 3.0 L/hr, which was the intended or prescribed flow rate. This increased flow rate is likely to explain the slightly higher clearance of ciprofloxacin by CVVHDF observed in this study, 2.4 +/- 0.4 L/hr versus 2.3 +/- 0.4 L/hr, given that the calculated ciprofloxacin sieving coefficients were similar for both studies. Similarly, a lower clearance by CVVHDF of 1.3 L/hr was reported by Malone et al (272), when a much lower effluent flow rate was employed.

A high ratio of C_{pmax}/MIC has been recommended for fluoroquinolones as an indicator of clinical and microbiological response. The mean C_{pmax} concentration achieved in this study was 5.6 +/- 0.9 mg/L. The mean C_{pmax}/MIC ratio, based on an MIC of 0.5mg/L, is 11.2. A C_{pmax}/MIC ratio of 8-10 is considered predictive of positive therapeutic response. The mean AUC_{0-24} was 59.0 +/- 17.2 mg.hr/L. This represents a mean AUC_{0-24}/MIC ratio of 118 +/- 34, based on an MIC of 0.5mg/L. A suggested characteristic of adequate dosing for ciprofloxacin is an AUC_{0-24}/MIC ratio > 125. The PK-PD parameters achieved by a dosing schedule of 400mg ciprofloxacin every 12 hours, as presented for each patient in Table 6.2.4 (Chapter 6), suggest that a dosing regimen of 400mg ciprofloxacin every 12 hours will achieve adequate serum concentrations in patients treated with CVVHDF at high ultrafiltration rates.

Wallis et al (6) used a dosing schedule of 200mg every 8 hours and the mean C_{pmax} concentration (following subsequent doses i.e. not initial doses) was 3.5 +/- 0.5mg/L. This dosing schedule achieved on average a C_{pmax}/MIC ratio of 7. The mean AUC_{0-24} achieved by the same dosing schedule of 200mg every 8 hours was 48.3 +/- 8.7 mg.h/L, equivalent to a AUC_{0-24}/MIC ratio of 96.6 +/- 17.4, on the basis of a MIC value of 0.5mg/L. Malone et al (272) reported a mean C_{pmax} of 3.9mg/L for three patients treated with 400mg ciprofloxacin every 24 hours during

CVVHDF therapy. The mean AUC_{0-24} with this dosing schedule was 56.8 mg.h/L, which represents a AUC_{0-24}/MIC ratio of 113.6, on the basis of a MIC value of 0.5mg/L. Comparison of the PK-PD parameters observed in this study with those reported by Malone et al (272) is difficult due to differences in the CVVHDF conditions. Higher CVVHDF clearances due to the use of higher effluent flow rates were observed in this study.

Wallis et al (6) reported lower C_{pmax} concentrations and AUC_{0-24} values with a lower daily dose of 600mg ciprofloxacin, compared to the 800mg daily dose used in this study. CVVHDF conditions in this study were similar to those reported by Wallis et al (6). Historically, the antibacterial activity of ciprofloxacin and other fluoroquinolones in animal models has consistently correlated with a high AUC_{0-24}/MIC ratio and efficacy has been demonstrated when the AUC/MIC ratio exceed 125. A clinical study (280) of nosocomial pneumonia in critically ill patients treated with ciprofloxacin found that with an AUC/MIC ratio >125, the probable clinical and bacteriological cure rates were 80% and 72% respectively, while these were 42% and 26% when the AUC/MIC ratio was <125. A further study of ciprofloxacin (281) in the treatment of nosocomial pneumonia in critically ill patients showed that the pathogen was eradicated for half of the patients with an AUC/MIC ratio >250 on the first day of treatment but that with an AUC/MIC of 125, the pathogen was only eradicated from one third of patients. The majority of the remainder of patients with an AUC/MIC ratio < 125 were clinical failures and showed stepwise increases in MIC, indicating that they were becoming resistant to treatment. On the basis of these pharmacodynamic studies, the dosing schedule utilised in this study offers advantages in terms of achieving better PK-PD parameters than those reported in two previous studies of ciprofloxacin during CRRT.

8.6 Estimating Drug Clearance by CVVHDF

A number of approaches to estimating drug clearance by CRRT have been proposed. The use of sieving coefficients is the most widely adopted method for estimating drug clearance by the filter. For some drugs, sieving coefficients have been reported in the literature, for example; gentamicin (0.8), cefuroxime (0.9), metronidzole (0.8). Where SC values are not available, the unbound fraction can be used as an estimate of the SC. Among the drugs examined in this study, the reported unbound fraction tended to overestimate the filter clearance for vancomycin, but resulted in good estimations of filter clearance for the aminoglycosides and ciprofloxacin. One limitation of this approach applies where the flow rates achieved differ from those recorded or prescribed. As clearance is calculated on the basis of knowledge of the SC and effluent flow rates, this will result in increased error, depending on the extent of the discrepancy. A discrepancy between the actual effluent flow rates achieved and those prescribed or recorded in the nursing notes was observed for all drugs analysed in this study. However, the mean differences for the aminoglycoside and ciprofloxacin patient samples were small. Overall, the estimated S.C. or unbound drug fraction and the prescribed effluent flow rates gave a good estimate of aminoglycoside and ciprofloxacin clearances due to CVVHDF and the estimate was further improved by using the actual measured flow rates (Table 8.3). The first column of data indicates the directly measured drug clearance due to CVVHDF, the second column indicates the measured effluent flow rate, the third column denotes an estimate of filter drug clearance calculated using the measuring sieving coefficient and the measured effluent flow rates, the fourth column gives estimates of CVVHDF drug clearance calculated using the unbound fraction of the drug and the measured effluent flow rate, the fifth column gives an estimate of clearance calculated using the same

value for the unbound fraction and the effluent flow rate reported in clinical notes. The final column indicates measured creatinine clearance by CVVHDF.

Table 8.3: Comparison of a number of approaches to estimating drug clearance due to CVVHDF.

Drug	Cl_{CVVHDF} (L/hr) (Drug Clearance)	Measured Effluent Flow rate (L/hr)	Calculated S.C. x measured effluent flow rate	fu* x measured effluent flow rate	fu* x effluent rate calculated from nursing notes	Cl_{creat} (L/hr)
Vancomycin	2.15 +/- 0.34	3.1 +/- 0.4	2.17 L/hr	2.48 L/hr	2.64 L/hr	2.25 +/- 0.34
Amikacin	2.86 +/- 0.41	3.5 +/- 0.6	2.92 L/hr	2.82 L/hr	2.80 L/hr	2.74 +/- 0.42
Gentamicin	2.32 +/- 0.33	2.7 +/- 0.4	2.30 L/hr	2.43 L/hr	2.44 L/hr	2.02 +/- 0.39
Ciprofloxacin	2.41 +/- 0.40	3.4 +/- 0.5	2.38 L/hr	2.38 L/hr	2.40 L/hr	2.70 +/- 0.3

* fu (fraction unbound) for vancomycin estimated as 0.8 based on literature reports
* fu for amikacin estimated as 0.8 based on Amikin SPC ('twenty per cent or less is bound to serum protein)
* fu for gentamicin estimated as 0.9 based on Genticin SPC ('< 10% is bound to plasma protein.')
* fu for ciprofloxacin as 0.7 based on range for protein binding quoted in Ciproxin SPC ('Protein binding is low (between 19-40%).

The impact of effluent flow rates on drug clearance, and indeed on creatinine clearance, by the haemofilter is reflected in the tabulated data. During amikacin and ciprofloxacin therapy, similarly high effluent flow rates were used, resulting in very similar values for creatinine clearance. However, CVVHDF clearance of ciprofloxacin was less than for amikacin, as the sieving coefficient calculated for ciprofloxacin (0.70) was lower than for amikacin (0.83) (CVVHDF drug clearance represents the product of the sieving coefficient and the effluent flow rate). The lowest mean effluent flow rate was seen in the patient sample treated with gentamicin and this is reflected in the lower creatinine clearance measurement for this sample. Although, the sieving coefficient for gentamicin was slightly greater than for amikacin, which is in agreement with reported protein binding values for

both drugs, the CVVHDF clearance for amikacin was greater due to the significantly higher effluent flow rates achieved in the amikacin patient sample. One of the original research questions posed at the outset of this study by ICU clinicians was whether there was a reduction in filter efficiency over time. We were unable to show any change in CVVHDF effectiveness over time. The circuit was changed at the earliest sign of a problem and if circuit use had been prolonged, perhaps a change in CVVHDF performance would have been detected. However, according to best practice guidelines, the circuit is changed before the filter itself becomes problematic and the mean duration of use was 50.4 hours, which is less than the manufacturer's recommended duration of 72 hours. Initial aminoglycoside adsoption to the filter was not clinically significant in our patient sample.

8.7 Relationships between Effluent Flow Rates, Drug Clearance and Creatinine Clearance

For creatinine and the drugs analysed, there were varying linear relationships between effluent flow rates and clearance. The relationship between flow rates and drug clearance was similar for both amikacin and gentamicin. The r^2 values were 0.842 and 0.745 for gentamicin and amikacin respectively. Slopes were similar for both drugs (0.759 and 0.760). The intercept was not significant for either drugs, which is consistent with CVVHDF as the major route of elimination for the aminoglycosides.

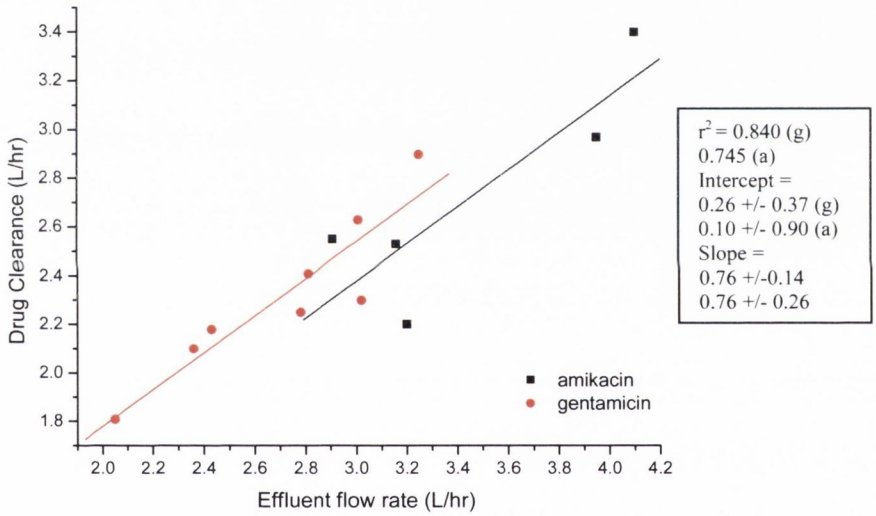


Figure 8.1: Aminoglycoside drug clearance versus effluent flow rates

For vancomycin, there was also quite a linear relationship between effluent flow and vancomycin clearance. The r^2 value was 0.668, lower than for the aminoglycosides. The slope was slightly lower than for the aminoglycosides but the intercept was still insignificant.

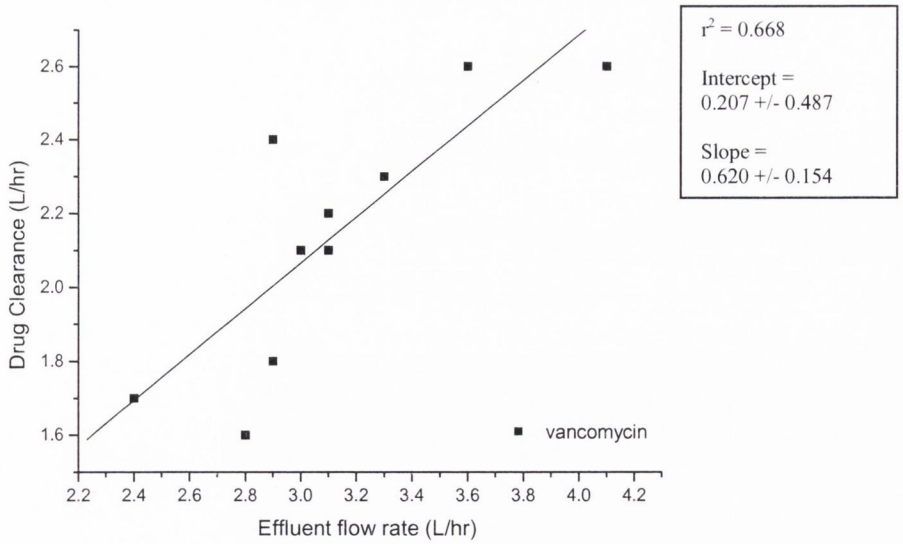


Figure 8.2: Vancomycin clearance versus effluent flow rates

For ciprofloxacin, there was a significant intercept, which is consistent with its metabolic elimination route. The r^2 was high; the value was 0.949. This suggests that effluent flow rates could be used to approximate ciprofloxacin clearance during CVVHDF, which is useful considering that ciprofloxacin serum concentrations are not monitored according to usual clinical practice

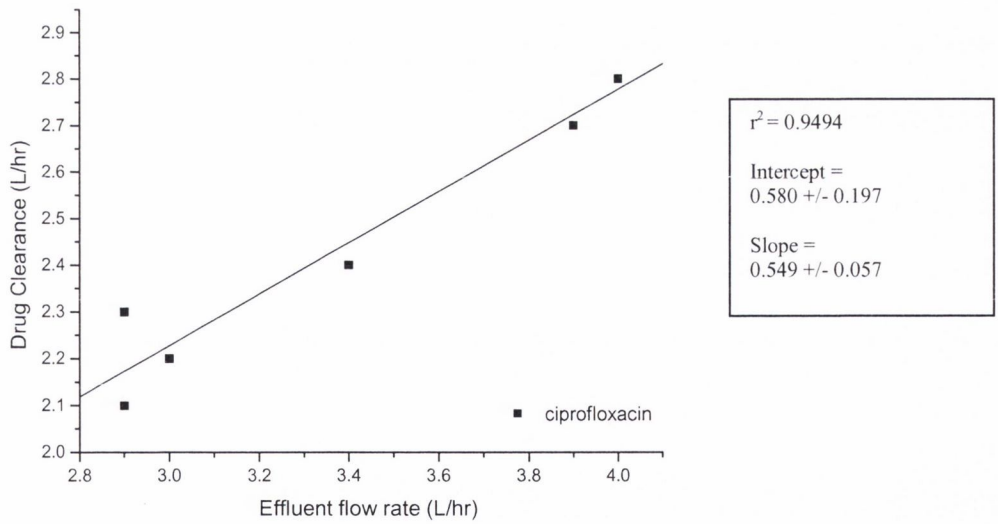


Figure 8.3: Relationship between effluent flow rates and ciprofloxacin clearance during CVVHDF

For creatinine, the intercept of creatinine clearance versus effluent flow rate was insignificant. The r^2 value was comparable to those seen with vancomycin and the

aminoglycosides. The slope of effluent flow rate versus creatinine clearance was higher than for any of the drugs analysed.

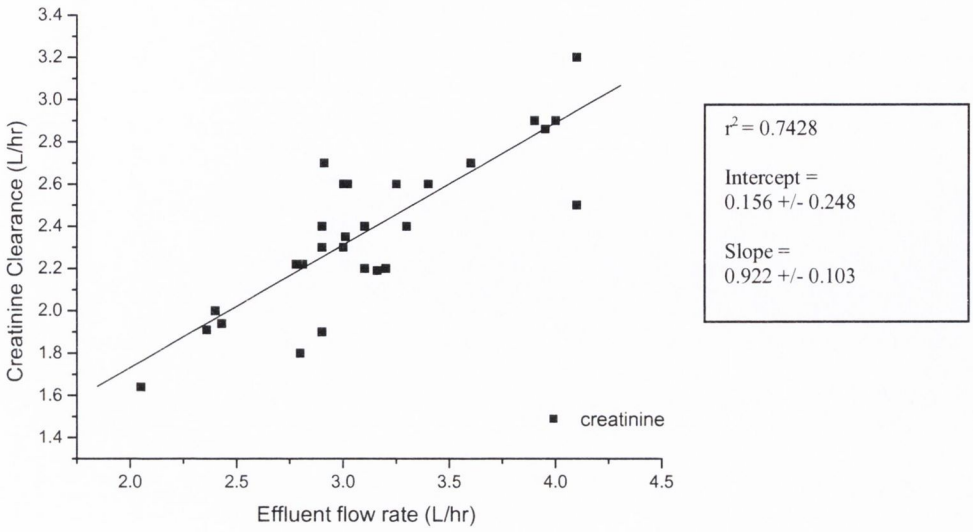


Figure 8.4: Effluent flow rate versus Creatinine Clearance during CVVHDF

There was a strong linear relationship between drug clearance and creatinine clearance. This supports the idea of using creatinine clearance by CVVHDF as an approximator of drug clearance by CVVHDF, where a drug is renally eliminated.

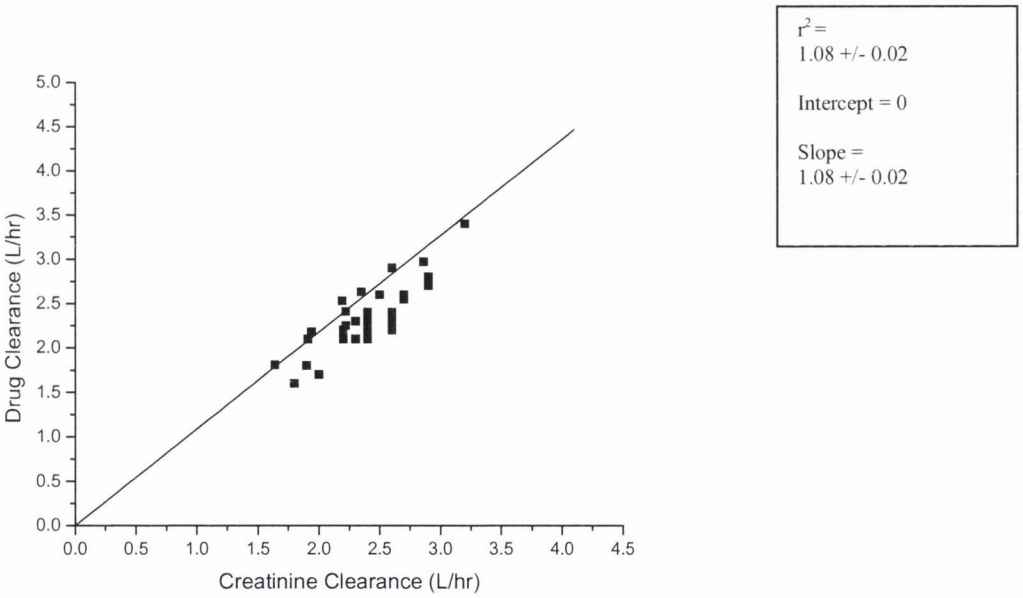


Figure 8.5: Creatinine clearance (L/hr) versus Drug clearance (L/hr) during CVVHDF

The correlation between TBC and filter clearance versus creatinine clearance by the filter was assessed for each of the individual drugs. The r^2 value for the correlation for vancomycin clearance due to CVVHDF versus creatinine clearance by the filter was 0.88 and the intercept was -0.4 L/hr. The r^2 value for the correlation between vancomcyin TBC and creatinine clearance was 0.71 and the intercept was -0.8 L/hr. These correlations are illustrated in Figure 8.6 and demonstrate a high correlation between creatinine clearance and vancomycin clearance by the filter. Creatinine clearance by the filter also correlates well with vancomycin TBC, conforming to the findings that (1) CVVHDF was the primary route of vancomycin elimination (2) Vancomcyin clearance due to CVVHDF correlates highly with creatinine clearance due to CVVHDF.

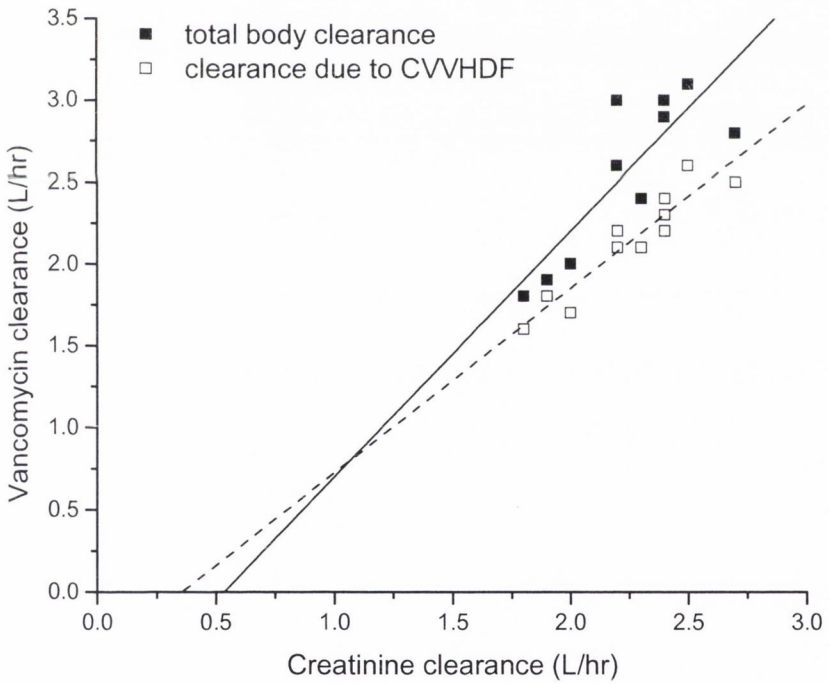


Figure 8.6: Creatinine clearance due to CVVHDF versus vancomycin clearance due to CVVHDF (- - -) and vancomycin total body clearance (—).

The fitted parameters (y=A+B*x) are given in Table 8.4 below:

Table 8.4: Fitted parameters for creatinine clearance by the filter versus vancomycin filter clearance (CVVHDF) and TBC.

Vancomycin	A	B	r	r^2
TBC (L/hr)	-0.8	1.5	0.84050	0.706440
CVVHDF (L/hr)	-0.4	1.125	0.93831	0.880426

The r^2 value for the correlation between aminoglycoside clearance due to CVVHDF versus creatinine clearance by the filter was 0.82, compared to 0.65 for the correlation between aminoglycoside TBC and creatinine clearance. These correlations are represented in Figure 8.7 and the fitted parameters for aminoglycoside TBC and clearance due to CVVHDF versus creatinine clearance are presented in Table 8.5. The correlation between creatinine clearance and filter clearance was similar to the correlation between TBC and creatinine clearance. Thus, CVVHDF clearance of aminoglycosides represents the major route of elimination and may be estimated by creatinine clearance by the filter. Creatinine clearance can be quantified by measuring creatinine concentrations in serum (midpoint) and effluent fluid together with effluent volume over a specific time period e.g. 12 or 24 hours. Consequently, creatinine clearance by CVVHDF can be calculated in a method analogous to 24-urine collection and can be used to estimate vancomycin/aminoglycoside clearance during CVVHDF. Requirements for dosage adjustment can thus be predicted on the basis of creatinine clearance by the filter, according to an individualised estimate of drug clearance under the CVVHDF conditions in use for a particular patient.

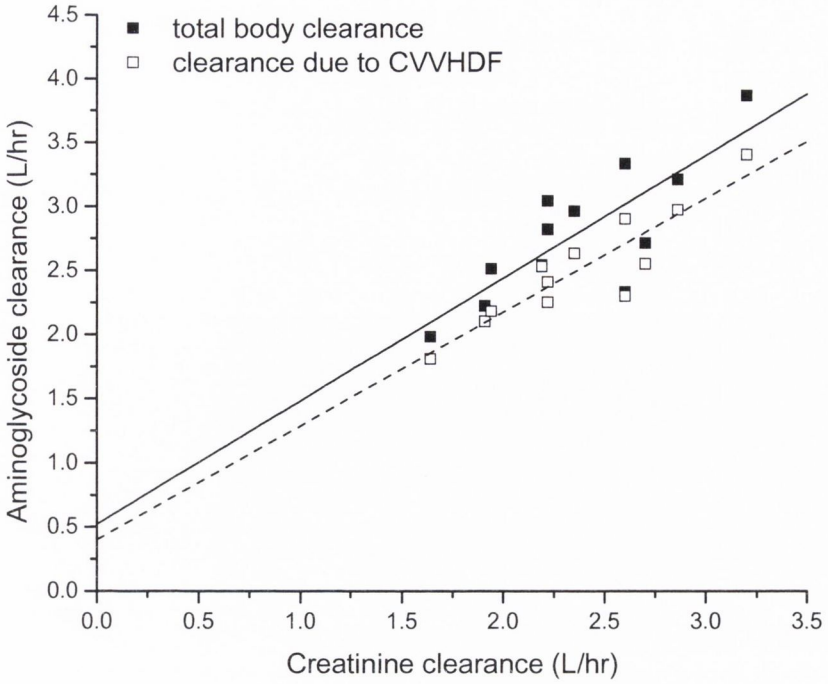


Figure 8.7: Creatinine clearance due to CVVHDF versus aminoglycoside clearance due to CVVHDF (- - -) and aminoglycoside total body clearance (—).

Table 8.5: Fitted parameters for creatinine clearance by the filter versus aminoglycoside filter clearance (CVVHDF) and TBC.

Aminoglycoside	**A**	**B**	**R**	**r^2**
TBC (L/hr)	0.52288	0.95816	0.80501	0.648041
CVVHDF (L/hr)	0.40074	0.88713	0.90644	0.821633

The r^2 value for the correlation between ciprofloxacin clearance due to CVVHDF and creatinine clearance by the filter was high (0.76). However, there was no correlation between TBC and creatinine clearance, indicative of the significant variability in the non-renal elimination of ciprofloxacin and the relative contribution of CVVHDF to TBC of ciprofloxacin among these patients. Figure 8.8 illustrates the relationships between creatinine clearance due to CVVHDF and ciprofloxacin filter clearance and TBC.

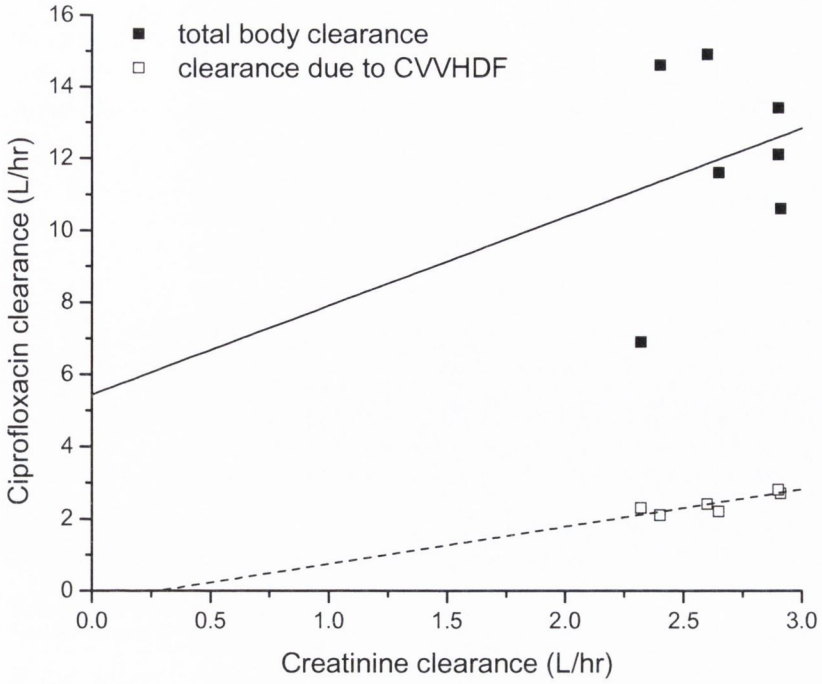


Figure 8.8: Creatinine clearance due to CVVHDF versus ciprofloxacin clearance due to CVVHDF (- - -) and ciprofloxacin total body clearance (—).

The fitted parameters for ciprofloxacin CVVHDF clearance and TBC clearance versus creatinine clearance are indicated in Table 8.6.

Table 8.6: Fitted parameters for creatinine clearance by the filter versus ciprofloxacin filter clearance and TBC.

Ciprofloxacin	**A**	**B**	**r**	**r^2**
TBC (L/hr)	5.43866	2.4641	0.22098	0.048832
CVVHDF (L/hr)	-0.2897	1.03469	0.87058	0.75791

As these correlations demonstrate, the contribution of CVVHDF to TBC varied predictably among the range of drugs studied. Table 8.9 represents a summary table of clearances indicating total body clearance, non-renal clearance and filter clearance for each of the drugs studied.

Table 8.9: Drug clearance summary table

Drug	**Total Body Clearance (TBC) (L/hr) mean +/- s.d.**	**Filter Clearance (Cl_{CVVHDF}) (L/hr) mean +/- s.d.**	**Non-renal clearance ($Cl_{non\text{-}renal}$) (L/hr) mean +/- s.d.**
Vancomycin	2.53 +/- 0.74	2.15 +/- 0.34	0.38 +/- 0.33
Amikacin	3.25 +/- 0.74	2.86 +/- 0.41	0.39 +/- 0.31
Gentamicin	2.83 +/- 0.45	2.32 +/- 0.33	0.45 +/- 0.32
Ciprofloxacin	2.40 +/- 0.41	12.02 +/- 2.83	9.54 +/- 2.76

8.8 Summary

In conclusion, CVVHDF effectively clears water-soluble, renally eliminated drugs such as vancomycin and the aminoglycosides, under the conditions analysed in this study. For ciprofloxacin, a drug with additional hepatic and intraintestinal routes of elimination, the contribution of CVVHDF to its total body clearance is reduced, but becomes significant where there is impairment of more than route of elimination. Patient factors, such as a changing Vd during CVVHDF, impact on drugs serum concentrations and require appropriate dosage adjustment. Changes in CVVHDF conditions such as effluent flow rates alter the magnitude of drug clearance due to CVVHDF. The use of sieving coefficients and effluent flow rates allows estimation of drug clearance, where effluent flow rates are accurately measured. The reported unbound drug fraction was similar to the calculated sieving coefficients for amikacin, gentamicin and ciprofloxacin, but was greater than the sieving coefficient calculated for vancomycin.

There was a linear relationship between effluent flow rates and drug clearance for the drugs analysed and a strong linear relationship between creatinine clearance and drug clearance.

Chapter 9. Conclusions

This project successfully quantified the effect of CVVHDF therapy on the pharmacokinetics of commonly prescribed antimicrobial drugs. Efficacious and aggressive treatment of infections during critical illness is essential for positive patient outcomes and this requires the application of pharmacokinetic and pharmacodynamic principles to prescribing decisions. CVVHDF was found to approximate 50% of kidney function in terms of clearance for vancomycin and the aminoglycosides. This finding was consistent with recent literature data on vancomycin, but there has been no published data on aminoglycoside pharmacokinetics during this particular form of CRRT. This data deficiency had led to subtherapeutic dosing of aminoglycoside antibiotics in this Hospital, prior to the implementation of our research findings.

This study established that routine therapeutic drug monitoring data, where peak and trough concentrations are monitored can be used to obtain useful estimates of aminoglycoside and vancomycin pharmacokinetic parameters during CVVHDF. These parameters can be used for appropriate dosage adjustment of these drugs for individual patients.

CVVHDF was found to be the primary route of drug elimination for the aminoglycosides and vancomycin. For ciprofloxacin, CVVHDF accounted for more than one fifth of total body clearance and up to one third of total body clearance in patients with concurrent hepatic and renal dysfunction. This finding was consistent with the metabolic component of ciprofloxacin elimination.

Effluent flow rates strongly impacted on drug clearance. Variability in literature reports of drug clearances by CVVHDF is likely to reflect differences in

CVVHDF conditions. A reasonably linear relationship between effluent flow rates and drug clearance was observed for all of the drugs analysed. Additionally, there was strong correlation between creatinine clearance by the filter and measured drug clearance. Drug clearance by CVVHDF was greater than previously reported for other forms of CRRT. A dose of 1g vancomycin i.v. every 24 hours provided adequate serum concentrations for most patients treated with CVVHDF. However, a shorter dosage interval is appropriate for patients with a high Vd or where high trough concentrations are indicated on the basis of M.I.C data. Dosing at intervals of the estimated half-life should avoid the problem of accumulation observed in previous studies.

The use of high doses of aminoglycosides, similar to those administered to patients with normal renal function, at extended dosage intervals, were necessary to obtain target PK-PD goals during CVVHDF therapy. A ciprofloxacin dosing schedule of 400mg twice daily achieved target C_{pmax}/MIC and AUC_{0-24}/MIC ratios during CVVHDF therapy.

CVVHDF therapy effectively contributes to drug clearance where there is a renal component to their elimination. Drug pharmacokinetics during CVVHDF therapy involves a complex interaction between patient, drug and CVVHDF system factors. Monitoring of drug serum concentrations, effluent flow rates and creatinine clearance by the filter, which allow estimation of drug pharmacokinetic parameters and clearance by the filter, contribute to an understanding of this interaction. This enhanced understanding of drug disposition during CVVHDF therapy has the potential to improve therapeutic outcomes of antimicrobial drug therapy and ultimately patient care.

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Appendix 1

PATIENT INFORMATION LEAFLET

Title of study: Pharmacokinetics of vancomycin, amikacin, gentamicin and ciprofloxacin in critically ill patients requiring continuous venovenous haemodiafiltration.

Introduction: Critically ill patients in the Intensive Care Unit are at risk of developing severe, life-threatening infections. To treat this, antimicrobial therapy is required. In addition, these patients are at risk of developing acute renal failure (kidney failure). Continuous venovenous haemodiafiltration (CVVHDF - a form of dialysis) is used in the Intensive Care setting to treat acute renal failure. There is very little data available as to the correct dosing regimen of the antimicrobials vancomycin, amikacin, gentamicin and ciprofloxacin used to treat sepsis in these critically ill patients who require this modality of dialysis. As a result, underdosing, resulting in inadequate treatment or overdosing, resulting in toxicity may occur. The purpose of our study is to evaluate the pharmacokinetics of these drugs in critically ill patients requiring CVVHDF. This will enable us to develop dosing guidelines for these antimicrobials, so that therapeutic levels are achieved.

The drugs under investigation will be analysed for the duration of the CVVHDF or to a maximum of five days if CVVHDF is required for a longer period.

Procedures: Intensive Care patients requiring continuous venovenous haemodiafiltration and treated with vancomycin, amikacin, gentamicin or ciprofloxacin for sepsis will be included in the study. Patients will be over 18 years of age. There is no therapeutic intervention in this study. Prescribing of antimicrobials will not be altered in any way during this study as a result of participating in it.

To analyse the drugs under investigation, serial blood samples will be taken. This will not involve the use of needles to obtain blood samples, as these critically ill patients will already have central venous access and arterial lines in situ. These venous catheters and arterial cannulas are required for monitoring purposes in these patients. It is possible to withdraw blood from these using a syringe only. There is no pain or discomfort to the patient.

Benefits: The results of this study will enable us to develop dosing guidelines for critically ill patients on CVVHDF requiring vancomycin, amikacin, gentamicin or ciprofloxacin for sepsis. This will minimize the risks of these patients being underdosed or overdosed with these drugs.

Risks: There are no risks to the patient as a result of participating in this study. Treatment will not be altered in any way.

Exclusion from participation: Patients under the age of 18 will be excluded from this study.

Confidentiality: Patients identity will remain confidential. The patients name will not be published and will not be disclosed to anyone outside the hospital.

Compensation: Your doctors are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

Voluntary participation: Patients are entered voluntarily in this study. They may quit at any time. It will not affect treatment in any way.

Stopping the study: The patient's doctor may stop the patient's participation in the study at any time without the consent of the patient.

Permission: The study has the approval of the hospital Research Ethics Committee. It also has the approval of the Irish Medicines Board.

Further information: You can get more information or answers to you questions about the study, your participation in the study and your rights, from your doctor who can be contacted through the Intensive Care Unit, Adelaide and Meath Hospital incorporating the National Children's Hospital.

Appendix 2

Aminoglycoside Volume of Distribution: Two-compartment model parameter estimates

Estimates of Amikacin parameters for Volume of Distribution calculated using a two-compartment model for patients treated with CVVHDF

ID	Vd_{ext} (L)	Vd_{area} (L)	Vd_{ss} (L)	Least sum of squares	MSC	r^2	Corr.
1	39.86	39.06	39.02	0.00492	3.01	0.9936	0.9736
2	39.02	38.36	38.24	0.00601	2.99	0.9895	0.9601
3	36.78	34.99	35.05	0.00549	2.97	0.9921	0.9754
4	33.31	31.98	32.27	0.00486	3.08	0.9946	0.9710
5	30.01	28.66	28.49	0.00512	3.02	0.9917	0.9812
Mean	**35.766**	**34.610**	**34.614**	**0.00528**	**3.01**	**0.992**	**0.972**
s.d.	**4.191**	**4.368**	**4.352**	**0.00048**	**0.04**	**0.020**	**0.008**

Estimates of Volume of Distribution for gentamicin calculated using a two-compartment model for patients treated with CVVHDF

ID	Vd_{ext} (L)	Vd_{area} (L)	Vd_{ss} (L)	Least sum of squares	MSC	r^2	Corr.
1	40.21	39.99	38.20	0.00408	3.22	0.9919	0.9795
2	38.07	37.08	36.12	0.00496	3.17	0.9894	0.9682
3	32.44	31.11	29.32	0.00487	3.10	0.9918	0.9755
4	30.04	29.65	28.04	0.00497	2.98	0.9922	0.9689
5	33.39	32.81	32.11	0.00542	3.11	0.9887	0.9641
6	31.08	30.06	29.38	0.0051	2.89	0.9881	0.9681
7	32.13	31.42	29.69	0.00427	3.24	0.9934	0.9792
Mean	33.91	33.16	31.84	0.00481	3.101429	0.990786	0.971929
s.d	3.78	3.90	3.88	0.00047	0.127466	0.002024	0.006082