

Pharmacovigilance and patient safety: lessons from nimesulide

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The suspension of a drug's authorisation because of serious adverse drug reactions (ADRs) has tragic consequences for patients and their families and it also raises important questions concerning the protection of public health.

Nimesulide is a non-steroidal, anti-inflammatory drug, whose authorised indications included the relief of the symptoms of osteoarthritis, painful joint disorders, such as tendonitis, post-operative dental pain and inflammation, and dysmenorrhoea.¹ It was suspended following 53 reports of cases of liver damage, including nine cases of liver failure in Ireland since its approval in 1995. There were four liver-related deaths in patients who had received nimesulide.²

Hepatotoxicity poses particular difficulties in the pre- and post-authorisation phases of drug development and it has caused more drug withdrawals than any other form of drug-related toxicity.³⁻⁶ Liver damage has been attributed to an enormous range of chemical structures among drugs. In most instances it occurs with therapeutic doses. It follows a variety of pathological courses. Which patients will be affected and in which patients it will progress to liver failure is hard to predict, even when monitoring liver function using plasma enzymes and other tests.

That is the general picture. What about the specific case of nimesulide? Almost all NSAIDs have been implicated in cases of hepatotoxicity, so it was not unique or unexpected, but it is a rare ADR (probability of between one in 10,000 and one in 1,000).⁵⁻⁷ Publication of the first detailed fatal case concerned an Irish patient in 1999.⁸ Several other cases followed quickly after that.⁹⁻¹² Other potential causes and predisposing factors for the hepatotoxicity have to be identified for optimal clinical management. In nimesulide's case, the rate of hepatotoxicity had been reported to be higher than for many other NSAIDs but also to vary between countries, possibly because of complicating factors or because of the way it was prescribed and used.⁶⁻⁷ This complex picture makes it less likely that hepatotoxicity will be attributed to a drug or solely to a drug and therefore less likely that it will be reported. The features of a case would be evaluated during follow up by the Irish Medicines Board (IMB) and used to assign a probability of causality by the drug to the ADR report. The presence of complicating factors such as those described above were reported by the IMB in two of the early cases of hepatotoxicity with nimesulide, thus reducing the probability of causality by nimesulide in those cases.¹³ Through the European Medicines Agency (EMA), the drug regulatory agencies of individual member states can seek a review of all the information

available about the drug, its use and its adverse effects within the EU. The EMA agrees upon a general course of action and each member state may take specific action. Sharing of information about ADRs is facilitated by the World Health Organisation's (WHO) monitoring centre (WHO).¹⁴ Nimesulide was licensed in around 50 countries but at the time of the EMA reviews in 2002 and 2004 it had been withdrawn from Spain, Finland and Israel. Ireland, on the basis of the interim results of a small observational study of Irish patients and the EU review, adopted the EMA approach and revised the Summary of Product Characteristics (SPC) and reduced the maximum recommended dose.¹⁵⁻¹⁶ These reviews and discussions among experts are confidential, since the material they cover could affect patient confidence and the commercial value of the products concerned.¹⁷ This confidentiality and the carefully worded statements that are released afterwards do not provide as much clinical background as healthcare professionals may need in order to make patient care decisions.

The SPC is the main source of information about a drug – it is derived from the information submitted to the IMB and is approved by them. When the SPC for nimesulide was revised in 2004, two recommendations were added to the 'special warnings and precautions for use' section:¹

- patients presenting with the symptoms of 'hepatic injury' were to be carefully monitored
- patients with abnormal liver function tests should have the drug discontinued

While nimesulide's ADRs were being reviewed, there were two other highly publicised clinical issues affecting the NSAID group: the gastro-intestinal (GIT) safety of the coxib group of COX-2 inhibitors (e.g. celecoxib) and the risk of thrombosis in patients taking NSAIDs. Nimesulide was initially considered selective for the COX-2 enzyme, although much less selective than the coxibs (COX-2:COX-1, nimesulide 5:1 to 16:1 compared to 400:1 to 800:1 for celecoxib, rofecoxib).¹⁸ However, by 1999 the IMB (and the EMA) classed nimesulide as a non-selective COX-inhibitor and amended the SPC warnings about GIT adverse effects to reflect its similarity to other non-selective drugs such as diclofenac, ibuprofen and naproxen, and in 2005 all of these drugs, as non-selective COX inhibitors, were considered a lesser thrombotic risk than the coxibs.¹⁹ These distractions meant that most healthcare professionals were following those studies and paying less attention to the possibility of nimesulide as a rare cause of hepatotoxicity. The lower thrombotic risk may have reassured practitioners that nimesulide was a suitable

alternative to the coxibs.

Some people have speculated that the fact that nimesulide was not registered in the UK or USA meant that there was something wrong with the drug. While this is not necessarily the case, the practical outcome of it was that a smaller population of patients in industrialised countries were exposed to the drug, so lessening the chances of uncommon ADRs being reported, and there were fewer current awareness bulletins and case study reports published in readily available journals. These two drawbacks were partially offset by the information disseminated within Ireland and by the WHO.

The IMB issues a drug safety newsletter which it circulates in hard copy and which is available via their website, www.imb.ie. Those featuring nimesulide can be accessed from the 'drug safety newsletter topics' link where an alphabetical listing is available.^{13, 15-16, 20} This is a crucial source of information since it contains the expert advice of the competent authority. A file of these newsletters should be kept in the pharmacy for consultation when a patient asks about the adverse effects of a drug.

The other source of medicines information in Ireland is the National Medicines Information Centre (NMIC). Its bulletins had covered rheumatoid arthritis (RA)²¹ and pain control²², but RA was not one of nimesulide's indications so it was not included, and the pain control bulletin focussed on the common properties of NSAID analgesics. The NMIC also issued a bulletin about ADRs²³ that provided general information and mentioned drug groups like NSAIDs, but did not highlight drugs of concern in Ireland. The WHO's pharmaceuticals unit and its ADR monitoring centre issued seven reports concerning nimesulide's status and ADRs in various countries between 1999 and 2005.²⁴⁻³¹ For a specialist in the fields of pharmacovigilance or medicines information this material would not be hard to find, but for a practitioner it is not readily accessible. The WHO pharmaceuticals newsletter reports on what is happening. It does not comment or offer guidance to practitioners. The dearth of information and advice about nimesulide from other sources made it crucial that the Irish sources had to highlight the drug's properties. Yet, anecdotally, it seems that most practitioners considered nimesulide to be a somewhat selective COX-2 agent and therefore to have a more favourable benefit-risk ratio for GIT and thrombotic adverse events.

But are the points mentioned so far sufficient to exculpate healthcare professionals from some responsibility? Nimesulide became one of the most frequently prescribed NSAIDs in Ireland³² so everyone was familiar with it. Some

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nimesulide patients were probably those who had reported GIT ADRs while taking other NSAIDs or were at risk of thrombosis, and so were prescribed nimesulide as a 'safer' alternative. Nimesulide had little to distinguish it from other NSAIDs, so its continued extensive use may suggest sub-optimal prescribing practices. The SPC recommendation to monitor patients with symptoms of 'hepatic injury' could be interpreted in a number of ways and probably did not convey the potential gravity and urgency necessary to encourage prescriber compliance with the recommendation. There is another issue, one that acts as a complicating factor to providing good quality care and to reporting ADRs, and also one that affects each of us in our professional practice. That factor is familiarity. It usually comes with a companion, complacency, and between them they rob us of the will and wit to act. For pharmacists, there is the extra barrier of establishing with the patient the pharmacist's role as a medicines advisor, not just a supplier. And with GPs and other prescribers the struggle to establish the 'right' to raise awkward patient- and drug-related problems.

What will happen now? The Joint Committee of the Oireachtas on Health and Children published a report on the topic of the Adverse Effects of Pharmaceuticals³³ earlier this year. Among its recommendations were, the need for more education at undergraduate and postgraduate levels about pharmacovigilance, and pharmacist-led medication review, especially in collaborative practice with prescribers, but, most strikingly, it suggested that the pharmacovigilance unit of the IMB should be established as an independent body. The Committee felt it was necessary to separate this activity from the rest of the IMB's work, which is funded by fees for product authorisation from Market Authorisation holders. It wanted a system for patients themselves to be able to report ADRs directly and for a Patient Safety Authority to be established. We do not know what the IMB's response to these proposals is, nor has the Commission on Patient Safety and Quality Assurance or the newly formed Health Information and Quality Authority yet made their views public. And, remarkably, there has been no response to date from either the Health Service Executive or the Department of Health and Children.

Patients' confidence and trust in the drug regulatory process, in pharmacovigilance and in the health service need to be restored. However, patient safety concerning drug use and pharmacovigilance are not the same; they do not have the same goals, nor do they use the same methods. What patients and healthcare professionals want are reassurance and guidance about best practice and the resources for implementation. And what pharmacovigilance needs is independence from the drug approval process, so that it can assume its central place in practice and in education in order to create the reporting infrastructure and culture that is missing in Ireland at present. More attention needs to be paid to communications about risk and about guidance for patient care in these situations¹⁷, since the present media and messages appear to be

largely ineffective, and the pharmaceutical industry has out-performed the public sector bodies in both of these areas.

More specifically, the suspension of oral nimesulide product authorisations may be lifted. The EMEA has rejected the option of withdrawing nimesulide altogether but has restricted treatment to no more than 15 days.³⁴ Whether this will be adhered to in practice, only time will tell. In the USA, the NSAID bromfenac was restricted to a ten-day treatment period, but in all 50 of the cases of severe liver injury that occurred, the patients had been treated for more than 30 days.³ The IMB's official response has not been published at the time of writing. (See Editor's note below)

And what should pharmacists do in the meantime? It is through precise routines of practice that good quality care is provided, following up non-specific symptoms to check for potential hepatotoxins, keeping accurate and up-to-date medication histories and using them, and being alert for ADRs, however unlikely they may appear. Patient care depends upon the implementation of these simple tools by alert individuals as much as upon the application of new technology.

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Editor's note: In an article written by Dr Muiris Houston, published in The Irish Times, Saturday 22 September 2007, Dr Joan Gilvarry, director of human medicines at the IMB, is quoted as saying, "Our concerns relating to the safety of nimesulide remain and we do not consider that the further restriction now proposed by the EMEA can ensure that nimesulide can be safely used."

Next Month: The role of the pharmacist in the monitoring and reporting of ADRs is examined from the practice perspective. What should we be looking out for and how do we act on our concerns?