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Nimesulide Controversy in India – Time to Learn

It was very distressing to learn about liver toxicities associated with the use of nimesulide in India.[1] It is a matter of great concern that serious and fatal adverse drug reactions (ADRs) of drugs in India are unnoticed and do not result in appropriate regulatory action because of the inadequate regulatory systems in that country, and because of this situation the Indian pharmaceutical industry is still able to take full advantage of marketing medicines that are withdrawn in Western countries.

Nimesulide is a relatively old drug with a Belgian-registered patent dating back to 1974. It is now mainly manufactured in India by a number of pharmaceutical companies and is described as a preferential cyclo-oxygenase (COX)-2 inhibitor. However, it was never marketed in the USA, UK, Canada or Australia because of its toxicity profile. Recently, the Finnish National Agency for Medicines withdrew nimesulide from the market following reports of liver toxicity and one suspected fatality in patients taking the drug. The death possibly linked to the drug was as a result of liver necrosis. The reports of liver toxicity were the basis of the decision to withdraw the drug. Spain has also recently withdrawn nimesulide, because of reports of liver toxicity. However, following reports of serious hepatotoxicity, especially in children, the Scientific Advisory Committee of the European Union issued a precaution on marketing of the drug.

In India, nimesulide was introduced in the early nineties and soon became the best selling anti-inflammatory drug. The product has sales in excess of Re (rupee) 2 billion (£24.5 million [sterling]; $US39.5 million) annually. It is marketed under more than 100 brands and in different formulations such as tablets, ointments and paediatric dispersible tablets and suspensions.

Nimesulide recently came under attack in India when a paediatrician at the prestigious Apollo Hospital in New Delhi reported the deaths of two children which were associated with the use of the drug.

When a new drug is licensed its adverse effect profile is incompletely known because only a limited number of healthy volunteers and highly selected patients have taken it. Thus, efficient postmarketing drug surveillance is needed. Unfortunately such surveillance does not exist or is inadequate in India.

To understand the prescribing indications for nimesulide, we looked at the various Summary of Product Characteristics or Patient Information Leaflet/package inserts. After a thorough search we could only manage to collect the package inserts from three pharmaceutical companies that market nimesulide. The indications for prescribing in children include fever and inflammatory symptoms associated with upper respiratory tract infections (viral or bacterial in origin) and reducing pain of various origins such as postoperative pain, pain due to musculoskeletal injury, pain due to soft tissue injury, etc. The most common adverse reactions listed in all these package inserts were gastrointestinal disturbances, e.g. heartburn, nausea, diarrhoea and vomiting, dermatological reactions (rash and pruritus) and CNS adverse effects (dizziness, somnolence and headache). It was surprising to note that none of the package inserts had listed hepatotoxicity as a common adverse reaction.

A literature search was conducted to find whether the pharmaceutical companies had conducted postmarketing surveillance on their product. After extensive search we found that there were five studies sponsored by Panacea Pharmaceuticals to determine the efficacy and safety of nimesulide.[2-6] However, none of these were postmarketing surveillance studies and ironically none of these studies reported any hepatotoxicity or abnormalities in the liver function tests.

The only other manufacturer of nimesulide to have conducted any studies was Dr Reddy's Labora-

tories. Dr Reddy's had conducted a country wide postmarketing surveillance study on nimesulide suspension,[7] and the authors were from the same company. It was surprising to know that of the 4097 patients, 261 (6.3%) were reported to have had an adverse event related to the use of nimesulide. The study was poorly designed and there were several flaws that needed much attention. The authors did not mention the age group of the patients, but stated that the objective of the study was to "investigate the recent concern that nimesulide may cause hepatic injury in children". There was also no mention how the doctors had assessed causality of these ADRs and what criteria were used for assessing causality. There were some serious ADRs reported in the study (although the authors did not categorise them as serious ADRs). For example, there were 13 cases involving renal disorders of which four cases each were of haematuria and generalised oedema, two cases each were of anuria and burning micturition and one case of nephritis. There were four cases of melena and one case of haematemesis (suggesting that there was gastrointestinal haemorrhage). There were also 29 cases of oedema of the face and eyes in this cohort of patients. All these reactions are considered serious ADRs according to definition of serious ADRs defined by WHO. On the contrary, the authors stated that because of the absence of any serious ADRs it is safe to use this drug in children. It was, however, surprising to note that there were only two cases of hepatitis in this cohort, which was in fact assessed as not possibly due to the drug.

In India, most doctor's get information about a product through the medical representatives. A study conducted by a pharmacist group based in Bangalore highlighted the limited knowledge of detecting and reporting of ADRs amongst doctors. It also showed that none of the doctors in that hospital knew that an ADR reporting centre existed.[8] These results are based in a modern urban hospital. If these results were to be extrapolated for the rest of the country, given that only one-third of the population of India reside in urban areas and nearly 70% reside in rural areas, the knowledge of doctor's practising in rural areas is likely to be far more inadequate. This study represents the gross under-reporting of ADRs by doctors due to limited knowledge.

India joined the WHO Adverse Drug Reaction Monitoring Programme based at Uppsala Sweden in 1998. In India there are three centres for ADR monitoring, a National Pharmacovigilance Centre located at the Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, and two WHO special centres at Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centres in turn report ADRs to the drug regulatory authority of India. The major roles of these centres is to monitor ADRs to medicines marketed in India; though they are hardly functional, as information about the need to report ADRs and about the functions of these monitoring centres is yet to reach the prescribers. There is also no common and proper ADR reporting form where the doctors can report any ADRs to the national centre in a systematic manner. The Indian Council of Medical Research has conducted few projects on ADR monitoring in India, but none of them have ever been published. Also there is not enough training imparted in this field to doctors in India. Therefore it comes of no surprise that not even a single report of ADR to nimesulide was reported by doctors to the national centre!

The regulatory authority of India, namely the Office of the Drug Controller General of India (DCGI), is responsible for approval of drugs, their safe use and marketing in India. In the wake of these safety issues concerning nimesulide, the DCGI ordered a high level enquiry and notified the manufacturers of nimesulide to submit all postmarketing surveillance data to the expert committee within a month. The expert committee had been ordered to look into all the data submitted by the pharmaceuti-

cal companies and decide the benefit/risk ratio as to whether nimesulide should be withdrawn in India. Nimesulide was under the Drug Therapeutic Advisory Board review for a long time. The DCGI was in fact made aware of ADRs associated with nimesulide use for the last 4 years.[9] Instead of making it mandatory for the pharmaceutical companies to conduct postmarketing surveillance to generate adverse event data on nimesulide and submit them to the regulatory authority, no action was taken. Instead, these companies promoted and marketed the drug and produced irrational combinations that are freely available in the Indian market, which could purchased over-the-counter without any prescription, to which the regulatory authority turns a blind eye.

Following this enquiry, the DCGI has gone on record to admit that due to powerful commercial interests, it might be difficult to get objective answers even from doctors. True to the anticipated fears, the Delhi Medical Association (DMA) has declared that nimesulide is a safe and effective drug! Criticising this act of DMA, leading paediatricians of India have questioned the validity of this survey from 50 doctors in Delhi on whose opinion the DCGI has given a clean sheet to nimesulide.

Given this situation, the Health Ministry of India needs to address the issue of withdrawing nimesulide immediately and making postmarketing surveillance mandatory for all pharmaceutical companies. "Dear Doctor letters" need to be issued to health professionals warning them about the hepatotoxicity associated with nimesulide use in children and adults. The Indian regulatory system needs to be strengthened and the pharmacovigilance system in India made effective by proactive monitoring of adverse drug reactions by the national monitoring centres, regulatory authorities of all the States, doctors and last but not least the pharmaceutical manufacturers. We think that the time has come to learn from past mistakes and build an effective pharmacovigilance system in India with the creation of an independent watchdog, that would keep an eye on the regulatory authority, pharmaceutical companies and prescribers to report adverse events to drugs.

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References

1. Unnikrishnan CH. Nimesulide ADRs on the rise, companies to phase out pediatric dosages soon [online]. Available from URL:www.pharmabiz.com [Accessed 2002 Nov 7]
2. Dhaon BK, Singh OP, Sharma S. Double-blind randomised comparative evaluation of efficacy and safety of nimulid (nimesulide) and diclofenac in osteoarthritis. Indian J Orthopaedics 1998 Apr; 32 (2): 91-3
3. Sharma VK, Srivastava R, Sharma S, et al. Comparative efficacy and safety of nimesulide vs piroxicam in osteoarthritis. Indian J Orthopaedics 1999 Jul; 33 (3): 212-6
4. Sharma S, Rastogi S, Gupta V, et al. Comparative efficacy and safety of nimesulide vs piroxicam in osteoarthritis with special reference to chondroprotection. Am J Ther 1999; 6: 191-7
5. Goyal PK, Chandra J, Unnikrishnan G, et al. Double blind randomised comparative evaluation of nimesulide and paracetamol as antipyretics. Indian Paediatr 1998 Jun; 35: 519-22
6. Roy V, Gupta U, Sharma S, et al. Comparative efficacy and tolerability of nimesulide and piroxicam in osteoarthritis with specific reference to chondroprotection: a double blind randomised study. J Indian Med Assoc 1999; 97 (10): 442-5
7. Srishyla MV, Sireesha K, Bhaduri J, et al. A country wide post-marketing surveillance of nimesulide suspension. Indian Paediatr 2002; 39: 310-1
8. Lakshmi PK, Gundu Rao DA, Gore SB. Doctors' preference for the location of a drug information centre leads to a hospital-based clinical pharmacy initiative in India. J Pharm Pract Res 2002 Sep; 32 (3): 240-1
9. Francis PA. Nimesulide review now? [online]. Available from URL:www.pharmabiz.com [Accessed 2002 Oct 9]