On the safety of nimesulide, a preferential COX-2 inhibitor

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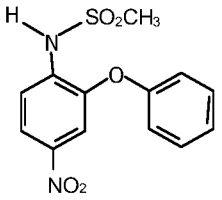
Nimesulide, a preferential COX-2 inhibitor is a non-carboxylic acid nonsteroidal anti-inflammatory drug (NSAID) that has been effectively used for the treatment of a variety of inflammatory and painful conditions, including osteoarthritis in European and Asian countries for more than 15 years. Its market share is reported to be fifth amongst the NSAIDs in the worldwide market[1]. It was introduced in the Indian market in the early 1990s. Unlike other classical NSAIDs, it has high gastrotolerability due to its relatively high pK_a value (6.5) and preferential COX-2 selectivity (COX-2/COX-1 = 0.19). This is perhaps one of the reasons (high efficacy and low gastric intolerance) that the drug is marketed in more than 50 countries, including India. There are more than 70 brands available in the Indian market. The drug is also available in a fixed dose combination with serratiopeptidase, a proteolytic enzyme and other classes of agents, but its combination with paracetamol needs critical evaluation as regards its rationality.

Chemical structure of nimesulide: Chemical name: N-(-4-nitro-2-phenoxy phenyl) methanesulfonamide; empirical formula: $C_{13}H_{12}N_2O_5S$; molecular weight: 308.31; CAS number: 51803-78-2.



Pharmacological basis of use of nimesulide

Nimesulide is chemically different from other drugs in this class because of the sulfonanilide moiety. Like all NSAIDs, nimesulide acts by inhibiting the synthesis of prostaglandins as a consequence of blockade of the enzyme cyclooxygenase (COX). Two isoforms of the COX isoenzyme are known, COX-1 and COX-2. COX-1 is constitutively expressed in most cells and elaborates prostanoids involved in various physiological processes, i.e. maintaining gastromucosal integrity and renal function (housekeeping functions). COX-2 is induced by proinflammatory cytokines and mitogens at sites of inflammation/tissue injury. Nimesulide has potent analgesic, anti-inflammatory and antipyretic activities on oral and rectal administration[2]. By respecting the activity of COX-1, nimesulide possesses a much lower risk for gastroduodenal lesions in comparison to classical NSAIDs. Nimesulide is reported to be a preferential COX-2 inhibitor in human blood assays (5–20-fold greater potency against COX-2 than COX-1). Besides COX-2 activity, nimesulide inhibits the production of oxygen free radicals, long-lived monochloramines, hypochlorus acid formed from activated neutrophils and other inflammatory cells. It is also reported to inhibit the release of histamine from the mast cells and basophils, and the production of PAF by neutrophils. Nimesulide has phosphodiesterase IV inhibiting property as well, and has antiprotease effect against neutrophil elastase, cartilage collagenase and stromelysin. The potent anti-inflammatory and analgesic activities of the drug are seen in a number of experimental models of inflammation, i.e. carrageenan-induced paw-oedema, adjuvant-induced arthritis, Randall Sellito test, UV-induced skin erythema and phenylquinone-induced writhing tests in mice[3]. In acute and chronic inflammatory conditions in patients, nimesulide is found to be more effective than placebo and had comparable anti-inflammatory activity with established NSAIDs. Epidemiological data suggested that long-term therapeutic use of nimesulide at anti-inflammatory doses (100 mg, twice daily) did not cause serious gastrointestinal symptoms. Nimesulide is also safe in aspirin-sensitive asthmatic patients. It is reported to be beneficial in relieving the symptoms of rhinitis, rhinopharyngitis, tubaritis and seceretory otitis media with concomitant antibiotic treatment.

Therapeutic indications

Because of its peculiar multi-factorial mode of action, nimesulide perhaps has demonstrably superior activities in painful and inflammatory conditions. It is mainly indicated for joint inflammation, osteoarthritic pain, fever, musculoskeletal conditions, acute pain including that from perioperative conditions, and dysmenorrhea. The daily-recommended dosage is 100 mg b.i.d. for these clinical situations.

Safety

Pharmacoepidemiological studies suggest that nimesulide is an effective NSAID with relatively favourable profile of safety for the treatment of osteoarthritis and non-rheumatoid musculo-skeletal conditions[4]. Clinically observed adverse events with nimesulide have been typical of those found with other NSAIDs[5]. Further, a post-marketing surveillance of nimesulide suspension (50 mg/ml), conducted through 600 pediatricians all over India, also indicates the absence of nimesulide-related hepatotoxicity in children[6]. The incidence of rare and unpredictable liver reactions with nimesulide is about 0.1 per 100,000 treated patients, which is not higher than most of the other NSAIDs[7] like diclofenac[8,9].

Further, the individual or inherent risk factors of the patient can predispose him/her to increased risk for development of nimesulide-associated unpredictable or idiosyncratic hepatic reactions. These include specific gene abnormalities, alteration in specific gene expression or epigenetic factors. The wide clinical efficacy with unique pharmacodynamic actions and beneficial gastrotolerability and bronchotolerability in comparison with other NSAIDs may outweigh the relative risk of nimesulide-associated liver reaction (common to the class NSAIDs) in the long-term use of the drug.

Present debate in India on nimesulide use

As stated earlier, nimesulide was introduced in the Indian market in the early 1990s for the management of pain, fever and inflammatory conditions. Recently, nimesulide has been under controversy due to alleged hepatotoxicity. Moreover,

the favourable efficacy and safety of nimesulide in different clinical situations in pediatric as well as adult population have been demonstrated by its virtual presence on the prescription in more than 50 countries, both developed and developing, in the last 17 years. Recently, controversial and ambiguous reports highlighted by the media on the grounds of isolated reported cases of hepatotoxicity without any known, conclusive and predictable drug-induced evidences have raised concern on the prescription use of nimesulide. The report of unexpected liver reaction to nimesulide may be viewed as a class phenomenon that occurs with all NSAIDs, including diclofenac, sulindac, etc.[10]. Many a times such adverse propaganda is market-force initiated. The present case is no different, if one analyses the global extent of its relative use and market share of the product.

In India, the sales of nimesulide oral solids have reached 1200 lac units of 10's with a consistent growth of 18% in the last three years, with Nise® and Nimulid®, being the two top-most leading brands. In an international survey (Brand Poll report) carried out on 300 doctors in Europe to assess the most recognized brands of anti-inflammatory drugs (product awareness), Nimesulide (Aulin®) not only ranked third in brand awareness, but it was also perceived as the most effective and one of the most safest drugs (perceived quality) in the NSAID market.

The safety profile of the drug is currently under review by the Committee for Proprietary Medicinal Products after temporary suspension in Finland, Spain and Turkey due to suspected serious drug adverse reaction. Helsinn, the first pharma company which had marketed the drug, is confident that nimesulide has a positive risk benefit profile, and will support such a concept with a group of top international experts in the ongoing discussion with European Agency for the Evaluation of Medicinal Products. Following the Irish Medical Board's 1999 review, the company was requested to perform post-marketing authorization studies to address the safety issues. A pilot study in 500 Irish patients suggested that the safety profile of nimesulide was similar to that of other NSAIDs. An observational study in 9000 Irish patients, comparing the safety profile of nimesulide with diclofenac and ibuprofen, the other two older NSAIDs, is currently under way. Interim data provided by the company on 1212 patients indicated that at this stage, there was no apparent difference in the safety profile of the three treatments.

Considering all the views of the alleged hepatotoxicity, the Drug Controller General of India (DCGI) has constituted a subcommittee of Drug Technical Advisory Board, a statutory body under the Drugs and Cosmetics Act 1940, Govt of India to review the clinical status of nimesulide. The sub-committee which met on 9 October 2002 has opined to obtain the views/experiences from a few leading manufacturing companies of nimesulide formulation in India, as to whether they have received any severe adverse drug reaction reports from their field force or from medical practitioners. Meanwhile, post-marketing surveillance data are also being collected. Two years ago, a debate on the irrational combination of paracetamol with nimesulide had also led to the ban of this combination by the DCGI[11].

Drug control issues which lead to marketing of irrational combinations

The Indian laws have not been properly defined to grant marketing approvals of the fixed dose combinations (FDCs) by state or central drug controlling authorities. Therefore, the state drug controlling authorities have continuously been approving various FDCs lacking any pharmacodynamic or pharmacokinetic advantages and acceptable rationale, for example, nimesulide–paracetamol combination, without prior permission from the DCGI. Such type of approval without any preclinical and clinical studies leads to marketing of prescription-based irrational combinations.

FDC products are those which have two or more drugs present in a fixed ratio, where one of the drugs either potentiates or synergizes the effect of the other, or the symptomatic relief provided by the two of them differs in nature in the same disorder.

As per Rule 122B, D, E(C) (Appendix VI of Schedule Y) of the Drugs and Cosmetics Act of India, FDCs fall into four categories:

(a) The first group includes those in which one or more of the active ingredients is a new drug.
(b) The second group includes those in which active ingredients already approved/marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.
(c) The third group includes those which are already marketed, but in which it is proposed either to change the ratio of the active ingredients or to make a new therapeutic claim.
(d) The fourth group includes those whose active ingredients have been widely used in particular indication for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience, and a stable acceptable dosage form, and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.

The groups (a)–(c) require adequate clinical data and the group (d) requires acceptable rationale that has to be submitted along with the application to get the marketing approval of FDC by DCGI, and not by individual state authorities. It may be of interest to mention that the model list of essential drugs prepared by WHO has only eight essential FDCs (WHO Technical Report 825, 1992), which would meet the medical needs of majority of the population.

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