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Regulatory Profile of Nimesulide with its Adverse Event in Europe and Rest of the World

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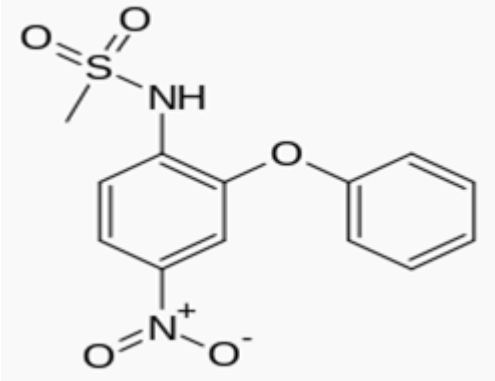
Abstract: ***All of the formulations are intended for the prevention or treatment of disorders and diseases, with just a few medications being lifesaving and necessary; the rest are interchangeable. Due to a lack of law enforcement and medical awareness, banned medications are nonetheless available in developing countries like India. Some of these medications, such as Nimesulide, Rofecoxib, Phenyl propanamine, and other OTC remedies, have been banned by the European Medicines Agency (EMA) due to side effects such as agranulocytosis, kidney and liver failure, and are still on the market. That wasn't outlawed until 2011 in India, which was too late because it was still legal for adults to use their despite its hepatotoxicity and potential drug interactions. [1, 37, 43] Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (cox –2) inhibitors are structurally heterogeneous drugs that share similar therapeutic actions and adverse effects. Hepatotoxicity, although a relatively rare adverse effect of this class of drugs, can be severe. These drugs have also been associated with idiosyncratic hepatotoxicity in susceptible patients. This has led to the withdrawal of some NSAIDs from the market. Nimesulide is an NSAID, with cox-2 preference, which has been reported to cause death from hepatic failure. However, most reports have been from European countries. Asian reports include that from Israel and India [4, 19, 21, 23, 38]***

Keywords: Nimesulide, Europe, India, Hepatotoxicity, Regulatory Profile, Adverse effects

1. Introduction

Nimesulide ($C_{13}H_{12}N_2O_5S$)

Nimesulide is a non-steroidal anti-inflammatory medicine that was discovered in 1971 and first sold in Italy in 1985. Nimesulide was never approved in the USA, United Kingdom, Canada, and New Zeeland. Considering Latin America, Argentina suspended nimesulide in all forms of presentation while in Brazil is widely prescribed and only contraindicated to children under 12 years old. Nimesulide is the only NSAID related to the arylsulfonamide class and is a "COX-2 preferential NSAIDs", because despite having a prevalent effect on COX-2, has a balanced action on bothcyclooxygenase. Nimesulide is rapidly absorbed into the synovial fluid, where it lasts longer than in the blood, contributing to the drug's pain-relieving effects. Early evidence suggestedthat cyclic AMP (cAMP) played a key part in nimesulide's anti-inflammatory activity; more recently, we discovered that the ecto-5′-nucleotidase/adenosine A2A receptor pathway is also involved This first extensive analysis of ADRs from a COX-2 selective NSAID, nimesulide, indicates that there is a relatively low incidence of ADRs especially in the gastrointestinal tract, while those in the liver are within or below the general incidence with other NSAIDs [2,3,14,22,26,36].



Nimesulide may harm the liver in a variety of ways, from asymptomatic increases in liver enzymes to jaundice, and it hardly ever results in death from liver failure. Hepatotoxicity is more likely in children receiving nemesulide. The severity of the liver disease may be the cause of nimulide-induced renal toxicity, or NSAID-induced interference with vasodilatory prostaglandins may be the cause, leading to unopposed renal arteriolar constriction. Creatinine, blood urea nitrogen (BUN), RBC, albumin, and bile salt levels in urine may all rise as a result of this. The DCGI has prohibited the use of Nimesulide in children under the age of 12 due to its well-known adverse impact profile.[29,32]

2. Mechanism of Action

With therapeutically relevant doses of nimesulide, the following effect occurs:

1) Prostaglandin synthesis inhibition :

Inflammation, pain, and fever are all caused by prostaglandins. There are two types of COX enzymes that produce prostaglandin. Almost all NSAIDs block both COX forms, therefore they have both positive and negative effects. The COX-1 enzyme, which is generally found in the gastrointestinal mucosa and kidneys, produces prostaglandins, which play a part in the body's defensive mechanisms. Inflammation triggers, on the other hand, cause the production of COX-2, which then produces prostaglandins, which contribute to pathological processes. The extensive knowledge gained in recent years about the mechanisms of cell death will undoubtedly lead to new and exciting advances in the prevention and treatment of liver diseases. [14,25]

2) Inhibition of the formation of toxic oxygen metabolites :
Toxic oxygen metabolites contribute to inflammation and pain. With human activated neutrophils in vitro, nimesulide substantially reduced the activity of the myeloperoxidase pathway, and to a smaller extent lowered hydrogen peroxide generation. Nimesulide also protected α1-antitrypsin from neutrophil-mediated oxidation, thus possibly attenuating the elastolytic activity of neutrophils.
3) Cytokine release :
The reduction of cytokine action by nimesulide seems to be unique among NSAIDs. In rats the drug inhibited the release of tumor necrosis factor α (TNFα) which governs the release of other hyperalgesic cytokines.
4) Histamine :
Nimesulide, but not indomethacin, decreased histamine-induced contractions in human isolated bronchial muscle and acetaldehyde-induced bronchoconstriction. [4,14,24,47]

Nimesulide Absorption

Following oral administration, the GI tract is well absorbed. Peak plasma concentrations: 1–3 hours. Within 24 to 36 hours after 100 mg of bid administration, steady-state is reached [10].

Nimesulide Metabolism

Nimesulide has a terminal half-life of about 4 hours, is quickly absorbed, and is tightly linked to albumin. There is very little unmodified medication eliminated in urine and faeces. The 4′-hydroxyl derivative, which is primarily eliminated from the body by metabolic transformation, is the main active metabolite of nimesulide (M1). In the dose range of 25 to 100 mg, nemesulide displays a linear pharmacokinetic profile when administered orally. The mosttypical dosage is 100 mg PO twice a day. The pharmacokinetic profiles of nimesulide and M1 in youngsters and the elderly are comparable to those in healthy young individuals. Nimesulide and M1 pharmacokinetics are unaffected by mild renal impairment [10].

Nimesulide excretion

Half-life of elimination: 2 to 5 hours. Metabolites in the urine: 80%; in the faeces: 20% of the amount given. 9% were attached to plasma proteins [10].

Adverse Effects:

- Gastrointestinal : epigastralgia, heart burn, nausea, loose motions
- Dermatological : rash, pruritus
- Central : somnolence, dizziness
- Hematuria is reported in few children
- Instances of fulminant hepatic failure have been associated with Nimesulide[17]

3. Literature Survey

Article Name	Year	Published Under	Conclusion
Fatal hepatotoxicity secondary to nimesulide	2001	SpringerLink	According to complaints made voluntarily to the World Health Organization, nimesulide causes a higher percentage of serious adverse hepatic responses than other NSAIDs recorded.
COX-2 selective nonsteroidal anti-inflammatory drugs: current status	2005	The Journal of the Association of Physicians of India	The production of vascular prostacyclin may be reduced by COX-2 inhibitors, which may also shift the scales in favour of prothrombotic eicosanoids and raisethe risk of cardiovascular thrombotic events.
Unregulated sale of Nimesulide in India	2009	Australasian Medical Journal	On the box, potential negative effects must be listed along with instructions to stop using the medication right away in the event that they occur.
Suspension of Marketing of Nimesulide containing medicines by IMB	2007	Pub med Journal	The IMB concluded that nimesulide was associated with an increased risk of liver toxicity compared with other anti-inflammatory treatments.
Assessment report for nimesulide	2012	European Medicine Agency	The CHMP came to the conclusion that nimesulide had a higher risk of liver damage than other anti-inflammatory drugs.
Survey on appropriateness of use of nimesulide in European Countries	2015	Dove press	Regarding indications, nimesulide was administered to numerous individuals who had either acute or chronic osteoarticular arthritis. These results show that the usage of nimesulide in the European nations taken into account in this survey is appropriate.
Nimesulide induced hepatotoxicity	2019	Pub med Journal	Our study's results confirm earlier reports that nimesulide use increases the risk of hepatotoxicity, and they add to the body of literature by supplying nimesulide risk estimates.

History

It was first commercialised in 1985 in Italy under the names Aulin and Mesulid, and it is now available in more than 50 countries worldwide. After choosing in March 2002 to temporarily remove the drug from the market due to reports of hepatic side effects in patients who were ostensibly treated with nimesulide, the EMEA evaluated the drug's benefit/risk profile in 2002. According to a 2003 study that was published in the British Medical Journal, the likelihood of hepatic reactions with nimesulide was later demonstrated to be comparable to that of any other NSAIDs.

As a result of allegations of serious liver damage, nimesulide was removed from the market in Finland and Spain in 2002. France had experienced cases at the time [20,24]

Numerous observational studies that evaluated the safety profile of nimesulide were published around the time that it was initially made illegal in a number of countries. Spontaneous reports from six Italian Regions collected from January 1990 to May 2005 were analysed . Retrospective cohort study in the Irish national liver transplant unit. All patients who received a liver transplant for fulminant hepatic failure of unknown cause, between January 1994 and March 2007, were evaluated. The European Medicines Agency (EMA) restricted the uses of nimesulide and its daily dose in 2004 . However, the Irish Medicines Board, the previous oversight body for the Health Medications Regulatory Authority, said in May 2007 that oral nimesulide-containing products were no longer approved due to a number of cases of fulminant hepatic failure[15,16, 28].

Failure necessitates liver transplantation. The EMA opted to approve continuing use of nimesulide after a second safety review of the drug was finished in 2012 on the grounds that the advantages of the drug outweighed the risks of liver toxicity . Contrary to popular belief, some members of the EMA's Committee for Medicinal Products for Human Use disapproved of this decision . Numerous regulatory actions to restrict the use of nimesulide have been taken in a number of European countries in response to heated discussion over its safety [4,5,6,7,8].

What prompted the nimesulide review?

Nemesulide was reviewed in 2007 as a result of worries about liver damage. Simulation studies were carried out to evaluate the effects of the regulatory measures concerning nimesulide on the overall number of hospitalisations for hepatopathies and upper gastrointestinal bleedings in Italy. According to experimental data, nimesulide causes oxidative stress, mitochondrial injury, and hyperplasia of the bile ducts in addition to hepatotoxicity. It also creates reactive metabolites that covalently change proteins. The Irish pharmaceuticals regulatory authority's decision to suspend the marketing authorization for treatments containing systemic nimesulide in May 2007 as a result of newly identified cases of fulminant hepatic failure necessitating liver transplantation served as the impetus for the review process. A database was created to record demographic information, clinical characteristics at the time of beginning, laboratory findings, suspected medicines, and follow-up. Clinical and lab data classified liver disease as hepatocellular, cholestatic, or mixed. The Committee determined that systemic formulations of nimesulide continue to provide more benefits than risks as long as their use is regulated to ensure that patients' chances of developing liver problems are maintained to a minimum. The Committee recommended that nimesulide only be used as a second-line treatment, that treatment duration be limited to no more than 15 days, and that packs should only be administered once[9,18, 26, 27,31].

What have the Committee for Medicinal Products for Human Use's (CHMP) findings been?

The Committee noted that research comparing nimesulide to other NSAID painkillers such diclofenac, ibuprofen, and naproxen in their ability to alleviate acute pain have shown that they are equivalent.

The Committee emphasised that nimesulide shares the same safety risk of causing stomach and digestive problems as other NSAIDs. Several limitations have already been implemented in the past to lessen the potential of side effects, the liver, including restricting use to second-line treatments, using the lowest effective doses for the shortest length of time, and setting a maximum treatment duration for acute pain[9].

The CHMP determined that nimesulide had a greater risk.

Regulatory Profile in India

In India, the Drug Technical Advisory Board (DTAB) has the last authority on whether or not to impose a ban. The DTAB receives reports from an executive committee that investigates the medications' negative effects. If a drug is discovered to have hazardous side effects, the government issues a ban order, instructing all manufacturers and wholesalers not to stock the drug. The DCGI informs all state drug authorities, pharmacist associations, and producers of the substance's prohibition. Inspections are to be carried out by authorities.

The Drug and Cosmetics Act allows pharmacists' licences to be cancelled if they stock forbidden substances. Packing has been standardised in order to ensure correct dispensing and reasonable usage of medications.

Even after a drug is approved for sale, its safety and efficacy are continually assessed based on data from pharmacovigilance, post-marketing surveillance, and information from other nations.

Inspite of world wide ban drug Nimesulide is being sold in India. [11, 30]

Pharmacovigilance System in India

Pharmacovigilance in India began in 1986 with the establishment of a formal adverse drug reaction (ADR) monitoring system under the supervision of the Indian drug controller.

India attempted but failed to join the World Health Organization's (WHO) Programme for International Drug Monitoring in 1998. In 2005, the National Program of Pharmacovigilance was established, and in 2010 it was renamed the Pharmacovigilance Programme of India (PvPI). The PvPI seeks to protect Indian citizens' health by ensuring that the benefits of medicines outweigh the risks associated with their use. The IPC-PvPI has been designated as a WHO Collaborating Centre for Pharmacovigilance in Public Health and Regulatory Services.

Despite these accomplishments, the PvPI has a number of obstacles, including monitoring generic pharmaceuticals, biosimilars, and disease-specific adverse drug reactions (ADRs) of antidiabetic, cardiovascular, and antipsychotic drugs, as well as raising awareness, which is a continuous effort. Simultaneously, the PvPI is attempting to address issues such as counterfeit pharmaceuticals, antimicrobial resistance, and surveillance during mass vaccinations and other national programmes. [12]

Pharmacovigilance System in Brazil
Health services, Marketing Authorization Holders (MAHs), and the sanitary agency are all involved in Brazilian pharmacovigilance legislation.

After the establishment of the National Agency of Sanitary Surveillance, which developed the Sentinel Network Project, drug tolerability began to be effectively assessed in Brazil.

The Sentinel Network Project's goal is to enhance the rate at which health care personnel report adverse drug reactions (ADRs) in the hospital setting. Brazil's pharmacovigilance regulatory improvements are only comparable to worldwide practices (ie, those of the European Union).

The European Union's pharmacovigilance system combines national authorities, the European Commission, and the European Medicines Agency, which is in charge of scientific review, supervision, and safety monitoring of medicines for human and animal use in the EU.

Significant improvements in pharmacovigilance regulation are expected as a result of Brazil's admission to the International Conference of Harmonization; these modifications, which will take into account international standards, will improve signal detection and risk communication.[13]

4. Discussion

The safety data provided support that nimesulide is associated with an increased risk for hepatotoxicity. Pooled data from epidemiological studies shows that nimesulide risk for hepatoxicity is comparable to ibuprofen, diclofenac and indomethacin, higher than for naproxen or ketoprofen and lower than for sulindac.

Results of the SALT study suggest that the (crude) incidence rate per billion DDDs for acute liver failure indicated for transplantation associated with nimesulide is higher than for celecoxib, diclofenac, ketoprofen, and naproxen and lower than for ibuprofen, paracetamol and indomethacin. Overall, nimesulide seems to have a worse safety profile for hepatotoxicity compared to diclofenac and naproxen.

5. Conclusion

- Nimesulide overall gastrointestinal toxicity is comparable to other NSAIDs but that nimesulide is associated with an increased risk for hepatotoxicity. The combined safety profile in terms of hepatotoxicity and gastro intestinal toxicity for nimesulide is shown as worse than some other alternative NSAIDs such as diclofenac and naproxen.
- Considering the maximum duration of 15 days of treatment to minimize the risk for hepatotoxicity and aiming a further minimization of the risks associated with nimesulide, the Committee considered that nimesulide use should be restricted to acute conditions only i.e. treatment of acute pain and primary dysmenorrhoea.

There is a risk of chronic use of nimesulide in “symptomatic treatment of painful osteoarthritis” and concludes that the risk-benefit balance of nimesulide-containing medicinal products for systemic use is no longer favourable in this indication

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