IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, January 2023
Impact Factor: 7.301

Nimesulide Induced Hepatotoxicity: A Review

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Abstract: *Nimesulide is a widely used drug for its therapeutic action . it is a selective cox-2 inhibitor belongs to NSAID group of drugs. But this drug is being lethal in some cases because of its hepatotoxicity. This study sought to assess the potential for hepatotoxicity associated with nimesulide, an NSAID that is sold in market.*

Keywords: Nimesulide, hepatotoxicity with nimesulide, nimesulide side effects

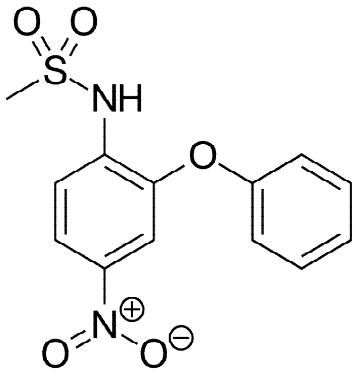
I. INTRODUCTION

Nimesulide is a selective COX-2 inhibitor. A post marketing assessment of 22,938 outpatients receiving short-term nimesulide therapy for osteoarthritis revealed that the adverse response profile of this drug is similar to that of other NSAIDs. Early research revealed that people with asthma who are aspirin-sensitive tolerate nimesulide well. Nimesulide has been taken off the market in various nations because to concerns over the benefit to harm ratio due to the numerous incidents of liver damage that have been recorded with it. For instance, in March 1999, the Portuguese Pharmacy and Medicines Institute banned the paediatric version of nimesulide. This choice was chosen in response to reports of severe medication side effects, such as liver damage, in young patients. If abnormal liver function tests start to appear, nimesulide should be stopped as away, and rechallenge should be avoided. The CPMP came to the conclusion that nimesulide has a favourable benefit to harm balance and that its marketing authorisation should be retained after reviewing the drug across the whole European Community. Nimesulide should only be used systemically to treat severe pain, according to the CPMP. Nimesulide users must be watched for signs of potential liver damage, and the medication should be stopped if tests or clinical results point to liver damage. It is unclear if this medication's propensity for hepatotoxicity is comparable to or greater than that reported with other NSAIDs.

1.1 Background

Nimesulide is a non-steroidal anti-inflammatory medication (NSAID) having analgesic and antipyretic actions that is mostly COX-2 selective. Its authorised uses include treating acute pain, osteoarthritis symptoms, and primary dysmenorrhea in adolescents and adults over the age of 12. The danger of hepatotoxicity has led to the withdrawal of nimesulide from the market in numerous nations. The therapeutic actions of nemesulide are the consequence of its full mode of action, which targets several important mediators of the inflammatory process, including histamine, free radicals, proteolytic enzymes, COX-2 driven prostaglandins, and free radicals.

1.2 Chemical formula $C_{13}H_{12}N_2O_5S$.



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The non-steroidal anti-inflammatory medicine nemesulide is the leading member of a novel family of sulfonanilides that has demonstrated a considerable inhibitory selectivity towards cyclooxygenase-2 without impacting cyclooxygenase-1. With an improved safety profile, this produces equal effectiveness against pain and inflammation. Patients who have allergic hypersensitivity to aspirin or NSAIDs seem to benefit most from nemesulide. Studies have proposed Nimesulide as a substitute for NSAIDs for those who cannot tolerate them.

There are hardly any instances of Nimesulide toxicity or negative effects. There is one report on six people who experienced severe liver damage after using Nimesulide, despite the fact that well-documented cases of acute hepatitis have not yet been associated with this medication. According to clinical and histological evidence, the pathogenic mechanism of Nimesulide-induced liver disease can be attributed to both immunological and metabolic idiosyncratic responses. Despite the fact that thrombocytopenia is a typical symptom of HIV infection, one group of medical professionals believed that the usage of Nimesulide was to blame for the thrombocytopenia in one of their patients.

According to a research, people who have atopy and a history of allergic responses to antimicrobial medications are more likely to develop sensitivity to nimesulide than people who have an allergy to NSAIDs. Researchers have looked at the risk factors for nimesulide intolerance in individuals with NSAID-induced skin diseases. Nimesulide drug interactions have been examined.

Nimesulide has the greatest risk of adverse effects among non-steroidal anti-inflammatory medicines, according to a review of significant hepatotoxic side effects reported to the World Health Organization (NSAIDs). This was discovered by Swiss researchers after they provided treatment for a 57-year-old lady with persistent lumbago who passed away from acute liver failure brought on by nemesulide. For the past few years, nimesulide's safety and side effects have been a source of debate. Patients with rheumatoid arthritis and osteoarthritis frequently use the medication. As a class, NSAIDs are notorious for their hepatic side effects. Analysis was conducted on unrequested reports received by the World Health Organization in connection to the overall number of reported adverse effects for any drug, including hepatic side effects. Compared to other NSAIDs authorised in Switzerland, mesulide causes a higher percentage of serious adverse liver responses. Hepatotoxicity, according to researchers at Zurich's University Hospital, is a significant risk factor for nimesulide use.

Nimesulide, like meloxicam, is a preferred COX-2 inhibitor; but, unlike rofecoxib, it is not a highly selective COX-2 inhibitor. NSAIDs are well-known and significant hepatotoxins.

The researchers found that of the 597 documented cases of nimesulide toxicity, 42 (7%) involved the liver. The odds ratio for hepatotoxicity caused by nimesulide relative to ibuprofen is 6.4

Assuming that the total number of complaints roughly matches the relative prescription frequency. This indicates that the risk of developing drug-induced liver damage is 6.4 times higher in nimesulide patients than in ibuprofen patients. Additionally, nimesulide's odds ratio is statistically greater than that of sulindac and diclofenac, two additional NSAIDs linked to a higher risk of hepatotoxicity. The unsolicited nature of these reports, together with the potential for bias on the part of medical experts, prompts the Swiss researchers to offer a word of warning.

According to the Swiss experts, there is no recognised mechanism for liver-induced illness. The liver processes nimesulide in great detail. Necrosis in the centrilobular area is the typical symptom of nimesulide-induced hepatocellular injury. Although still hypothetical, a certain genetic disposition may favour the creation of aberrant metabolites that either directly cause toxicity or trigger an immune response.

Substance-induced acute hepatitis is a well-recognized side effect of numerous medicines, including nimesulide, according to Israeli experts who have also investigated the drug. It is crucial to pinpoint a medicine as the root cause of this fatal condition since stopping the drug might save lives.

A 54-year-old Arabic lady with chronic back pain who was using nimesulide was taken to the hospital with severe hepatitis, which was later verified by biopsy. Within a month of stopping nimesulide, her liver function test results were normal. A test for in-vitro lymphocyte toxicity established that exposure to nimesulide was the cause of the liver damage.

The researchers found that, despite the low incidence of clinically significant liver damage brought on by NSAIDs, increased usage of these medications can nonetheless harm the liver. From modest aberrant liver function to severe liver lesions, nemesulide can induce a variety of liver ailments. On medication termination, these side effects are often reversible; however this is not always the case.

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A 54-year-old Arabic woman who was using nimesulide for chronic back pain was admitted to the hospital with acute hepatitis, which was subsequently confirmed by biopsy. Her liver function test results returned to normal after she stopped using nimesulide in a month. The liver damage was proven to be caused by exposure to nimesulide by an in-vitro lymphocyte toxicity assay.

The researchers discovered that increasing use of these drugs can nonetheless affect the liver, despite the low prevalence of clinically significant liver damage caused by NSAIDs. Nemesulide can cause a range of liver disorders, from mild abnormal liver function to serious liver lesions. These adverse effects are frequently curable after stopping the prescription, although it's not always the case.

Helsinn claims that as a sulphonanilide analogue, it is unrelated to traditional NSAIDs, which often include a carboxyl or hydroxyl functional group. Nimesulide, according to Helsinn, has been shown to be safe and effective in the treatment of a variety of inflammatory and painful ailments, including osteoarthritis, extra-articular diseases including tendinitis and bursitis, post-operative pain, and primary dysmenorrhea. Because of its comprehensive mode of action, nimesulide targets a variety of important mediators of the inflammatory process, including histamine, free radicals, and COX-2-mediated prostaglandins. Nimesulide is a non-steroidal anti-inflammatory, analgesic, and antipyretic medication having a particular mechanism of action, according to Helsinn, the Swiss pharmaceutical firm that controls the worldwide rights for its commercialization.

Riker 3M's discovery of nimesulide is presently sold by several brand names in 44 nations. With as many as 84 brands, Nimesulide generates 190 crore rupees in annual sales in India. The 19 nimesulide combinations are not included in the turnover. It is unknown how many generic nimesulides are offered, but given how frequently it is prescribed, there may be many more.

A source in the industry claims that nimesulide oral's annual sales in India total Rs 14.63 crore with a yearly rise of 2.8%, while the liquid form's sales are Rs 21.70 crore with a growth of 13.8%. Children's liquid doses are intended however there shouldn't be any adverse effects as they are only consumed for a brief time. "Recently, there have been more reports of negative side effects related to nimesulide use. The possibility of hepatic adverse effects following nimesulide exposure is a persistent worry. According to a report, the use of nimesulide resulted in two fatal liver failures. Additionally, nimesulide increases the hepatic dysfunction brought on by any of these medications when combined with amoxicillin and clavulanate "The WHO ADR Newsletter published a newsletter in December 1999 from the National Pharmacovigilance Centre at the Department of Pharmacology of the All India Institute of Medical Sciences. Infarmed, the Portuguese Pharmacy and Medicines Institute, halted paediatric presentations of nemesulide after the National Pharmacovigilance Centre (CNF) of that nation received significant ADR complaints that included included hepatic responses, according to an April 1999 Scrip report. In that nation, where four brands of NSAIDs are sold in addition to Helsinn's own Aulin, there were three fatal occurrences. Although a direct causative connection with the administration of nimesulide is difficult to prove, the possibility cannot be ruled out, the research stated. The paediatric dosages are exclusively offered for purchase in Italy.

Indian physicians who have used nimesulide have different opinions on its effects. Dr. Anand N. Malaviya, a rheumatologist in Delhi, claims that nimesulide is used by the majority of arthritis sufferers. Additionally, the liver enzyme level is often high. "It got to the point where I could scarcely begin giving them methotrexate right soon. I had to continue to wait before taking the medication. I have been warning my students and coworkers not to take it, especially if we intend to provide the rheumatoid arthritis medications methotrexate and/or leflunomide. I have remained committed to this position throughout. I would much prefer provide a brief course of steroids than NSAIDs, particularly nimesulide, because doing so would prevent me from being able to administer the rheumatoid arthritis life-saving medications methotrexate and/or leflunomide."

Helsinn is attempting to obtain US FDA and UK MCA clearance, according to the medical director of a global corporation. "The US FDA's approval process is pretty straightforward: If the medicine is not the first of its kind, they must demonstrate a meritocracy. That is, whether it has higher effectiveness and less negative effects. They must demonstrate if it is pharmacoeconomical if both are identical. Helsinn has failed to demonstrate either in the instance of nimesulide."

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"Since quite some time, nimesulide has occasionally been mentioned in reports of liver damage. While such reports were few, we also learned that it was nephrotoxic in between. In any event, all NSAIDs are hazardous to the kidneys "An Indian pharmaceutical company's medical advisor told this correspondent.

There is, according to a senior industry insider who has long been involved with the generic variants of the chemical, a severe dearth of public English-language information on nemesulide. "It is not an extensively used chemical. When compared to diclofenac, which causes acidity, nimesulide does not have rapid adverse effects, but its hepatic effects gradually manifest over time. Even though it is dangerous and nonsensical, nimesulide and paracetamol combos are now routinely accessible in this country. The drug controller general of India has to cease selling these products immediately."

A top rheumatologist recently claimed that leflunomide and NSAID combo treatment had a side effect. Leflunomide received a poor rap, although the NSAID was fully to blame for the adverse effect, he claimed. It should be mentioned that nimesulide is frequently used to treat arthritis.

II. CONCLUSION

By giving risk estimates for nimesulide-associated hepatotoxicity, our work adds to the body of literature and supports using nimesulide increases the risk of hepatotoxicity. More research are required to fully define the effects of dosage and duration of therapy on the risk for hepatotoxicity because the analysis only included a small number of studies, the majority of which used observational study designs.

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