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Review Article

THE CONCEPTS AND PROSPECTS OF NIMESULIDE INDUCED HEPATOTOXICITY

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed class of drug. The current study was carried out to reveal the facts and prospects of Nimesulide, an over-the-counter NSAID drug. Around 57 cases of hepatotoxicity collected from the DILI registry in Spain and Latin America were reviewed. Various causality cases were assessed using the RUCAM scale, which revealed the mean age of 59 years of patients among the entire case series of hepatotoxicity, out of which 86% were women, and the mean onset time of action was 40 days, while 46 patients, i.e., 81%, were also suffering from jaundice. Nimesulide-induced liver injury was found to be hepatocellular in 38 cases (67%), mixed type in 12 cases (21%), and cholestasis in 7 cases (12%). The reported incidence of NSAID-induced liver disease in clinical trials was found to be fairly constant, ranging from 0.29 per 100,000 [95% confidence interval (CI): 0.17-051] to 9 per 100,000 (95% CI: 6-15). Therefore, a higher risk of liver-related hospitalisation (32.3 per 100,000 patients) was reported. The studies indicated that Nimesulide and other NSAIDs cause extensive liver damage, ranging from asymptomatic transient hyperaminotransducers to fulminant liver failure. However, various shortcomings in epidemiologic studies jeopardise the opportunity to determine the actual risk of hepatotoxicity. The drugs, such as Benoxaprofen and Bromfenac, have been withdrawn from the market due to their hepatotoxic behaviour. The present review was carried out to critically analyse the results currently available in the literature on NSAID-induced hepatotoxicity and to create an overview of the most commonly used compounds of the NSAID groups.

Keywords: Liver damage, Liver injury, Hepatitis, Hepatotoxicity, Nephrotoxicity, Non-steroidal anti- inflammatory drugs.

1. INTRODUCTION

NSAIDs (non-steroidal anti-inflammatory drugs), the most commonly used drugs worldwide, have miscellaneous uses but are mostly used in the treatment of various inflammatory diseases such as allergies, atherosclerosis, arthritis, and many more. It also relieves acute pain, fever, and chronic and subchronic chronic situations [1]. These drugs can be administered by oral, parenteral, transdermal, and suppository routes; their duration of administration varies from a single dose to long-term therapy, and their variable dosage depends on the nature of the indication (low to high dose), on monotherapy, or in combination with other drugs (such as paracetamol). NSAIDs can be classified as preferred COX-2 inhibitors, selective COX-2 inhibitors, non-selective COX-2 inhibitors, antipyretics, analgesics, and agents with weak anti-inflammatory effects, among which Nimesulide has strong anti-inflammatory effects [2]. Proven applications include the treatment of osteoarthritis, acute pain, and primary dysmenorrhea in adults aged 12 years and older and adolescents. The effects observed may be related to liver problems. The drug has a complex mode of action determined by a rapid onset. It blocks the production of prostaglandins (pain-related chemicals), causing a reduction in pain and inflammation. In March 2002, Finland suspended the marketing of Nimesulide due to the high incidence of hepatotoxicity associated with its use. This was followed by Spain in May 2002, but other European countries such as Italy and France did not prohibit its usage. Nimesulide was withdrawn from the Finnish and Spanish markets due to reported liver toxicity but was still available with a modest increase in risk. India's Drug Enforcement Administration is reluctant to ban Nimesulide outright,

which should be taken seriously. The drug is sold in around 50 countries. It is most commonly prescribed in Italy (which accounts for half of the global market) and Portugal (which reports approximately 10% of drug-induced liver injury). The estimated incidence of NSAID-induced hepatotoxicity is variable and ranges from 0.29 to 9.0 per 100,000 patients per year [3]. In the present review, we have compared the incidence of acute hepatotoxicity associated with Nimesulide and other NSAIDs.

2. EPIDEMILOGY

Epidemiological studies evaluating severe NSAID liver toxicity include hospitalisations and deaths in exposed populations. Data from England indicates that the frequency of NSAID written prescriptions has somewhat changed since 2001, i.e., a 4% decline in consumption of Diclofenac and a 5% increase was observed for Naproxen, which is a relatively weak Cox inhibitor. Preferably used Cox-2 inhibitor Nimesulide, an NSAID, has analgesic and antipyretic properties [4-5]. An important pitfall in demonstrating the risk of NSAID-induced liver injury lies in the design of epidemiological studies. In general, the strengths of randomised controlled trials (RCTs) are close follow-up of patients, comparisons with control groups, and accepted designs to demonstrate the efficacy of a particular treatment. However, RCTs often represent only general population samples and are seldom truly representative, especially as evidence for the development of hepatotoxicity [6]. Furthermore, studies on populations under 18 years of age are often inconclusive, as they are usually underestimated unless explicitly excluded [7]. Instead, data on the incidence of hepatotoxicity in cohort studies, case-control studies, and other studies are not unbiased. Viral infections, environmental factors, metabolic factors, and alcohol abuse coexist with mixed DILI data.

Similarly, retrospective studies have significant drawbacks, such as investigators ignorance of the co-administration of drugs other than investigational drugs. Another important limiting factor that affects both pre- and post-marketing studies of hepatotoxicity is the fact that mild and resolvable cases are underreported. The next reason for failure is the lack of a reliable "denominator" (defined as the number of potentially exposed patients). The other parameter for the underestimation of hepatotoxicity can be considered to be timely reporting, or the delay between the occurrence of adverse events and the reporting of cases. The latter should be considered when anxiety is accompanied by severe liver damage. The incidence of NSAID-induced liver disease studied in most studies is uniformly constant (1-9 cases per 100,000). Traversa and his colleagues analysed a retrospective study from 1997 to 2001 in a region of Italy with a population of 850,000. Which approximately 2 million prescriptions from patients treated with NSAIDs over a five-year period were analysed. The findings of this study indicated very low hepatotoxicity associated with the use of NSAIDs (using prescription as the denominator); the frequency of liver injury was 1.7 per 100,000. In contrast, higher levels of hepatotoxicity were observed in people older than 75 years (they had a 5.7-fold increased probability of liver disease as compared to younger ones, i.e., 45 years). Interestingly, Nimesulide had a slightly higher incidence of liver damage and a higher hospitalisation rate than other NSAIDs (i.e., 33 per 100,000 patients per year versus 22 per 100,000 patients per year).

The large number of enrolled patients and extensive follow-up were the positive features of this study. On the contrary, a case-control study including all the marketed NSAIDs indicated that Diclofenac was the drug associated with the surge of liver damage (95% CI: 1.9-8.8) [10]. Further Lane and his colleagues reported the largest randomised, prospective, double-blind study involving patients, which increased by four times and whose results were found to be comparable. Concomitant side effects of the drug required hospitalisation, i.e., 23 out of 100,000 patients. They also noted that symptoms of Diclofenac-associated liver disease occur sooner or later after the initiation of drug treatment [11]. The results showed a low diclofenac-related hospitalisation rate and a very low rate of cardiovascular events. In fact, 132 patients with aminotransferase levels >3 the upper limit of normal (ULN) were single women who required hospitalisation for hepatic disorders. Rostometal used the MEDLINE and EMBASE bibliographic databases, and the FDA identified randomised controlled trials of Naproxen, Diclofenac, Ibuprofen, Rofecoxib, Celecoxib, Valdecoxib, or Meloxicam in adults with rheumatoid arthritis or osteoarthritis. The authors analysed aminotransferase elevations above ULN 3, liver-related hospitalisations, drug discontinuation, serious adverse events, and liver-related deaths [12]. The 65 database articles and 67 FDA-submitted studies were analysed, and the conclusion was that Roxecoxib and Diclofenac had higher transaminase levels compared to placebo and other NSAIDs studied. Interestingly, none of these studies reported a high incidence of serious adverse events relating to the liver, hospitalisations, or death,

except one with naproxen. This very low hospitalisation rate is 3/100,000 patients (0.5-15/100,000 patients).
Of the 51,942 patients who took NSAIDs, single patient died from naproxen hepatotoxicity. Mortality was also low at 2/100,000 patients. These results are consistent with the results reported by Rubenstein and Laine, who analyzed multiple epidemiological studies to determine the risk and incidence of severe liver-related NSAID toxicity [13]. Seven studies met the criteria suggested by authors. It was observed that rates of hospitalization related to hepatotoxicity in three cases i.e. 1-23.4/100,000 patient per years for current NSAID use and 4.8-8.6.6/100,000 patient per years for previous NSAID use increased the risk. Additionally, these investigators recorded no NSAID-related mortality when analyzed cumulatively in 396,392 patients per year. Much of the information on the incidence and relative risk of NSAID-related hepatotoxicity comes from cohort or case-control studies, which usually have a low incidence of hepatotoxicity. Much effort has been expended to identify clinical factors that predict drug-induced severe liver injury [14]. Several years ago, the FDA formed a task force with representatives from the Pharmaceutical Research and Manufacturers of America (PhRMA) and the American Society of Liver Diseases (AASLD) to investigate ways to minimize the risk of hepatotoxicity [14]. Despite valuable efforts, no expert consensus could be reached on clinical parameters that can predict severe liver injury. However, we still use transaminase levels >3-fold higher than the ULN as a marker of significant hepatocellular injury [15]. There are several other alternatives available in market.[16]With respect to Indian marketNimeulide is not only the drug causing liver toxicity, infect several studies have indicated other drugs higher incidence as compared to Nimesulide (Table 1) [17].

Table 1: Liver related hepatotoxicity induced by NSAIDS

Drug	Pattern of Liver damage	Mechanism	Incidence
Nimesulide	Acute Hepatitis, Pure Cholestasis	Metabolic	Moderate
Diclofenac	Acute & Chronic Hepatitis, Reye's Syndrome	Dose dependent	Low
Ibuprofen	Ductopenia, Acute hapatitis	Metabolic	Low
Naproxen	Cholestatic Mixed damage	Metabolic	Low
Coxibs	Acute Hepatitis also Mixed Damage	Metabolic	Low

3. NIMESULIDE

Nimesulide has an anti-inflammatory, antipyretic, analgesic, and anti-inflammatory effect due to its potent inhibitory effect on the COX-2 enzyme. The drug is well tolerated in the gastrointestinal tract. The mechanism of action has been assigned to the chemical structure of the class of sulfonanilides [18]. In 1997, as per the literature, one of the groups in Argentina reported the first observation linking Nimesulide and hepatotoxicity [19]. Since then, there have been consistent reports of severe hepatotoxicity until the national health authorities of several countries withdrew Nimesulide from the market [20-21]. Nevertheless, the drug is still marketed in several European countries, but the EMEA report recommends limiting the duration of treatment to 15 days and limiting the drug use, i.e., the maximum dose, to 100 mg per day [3]. The controversy surrounding Nimesulide continues, and a series of clinical reports and epidemiologic studies continue to focus on the drug's role in severe liver injury [22]. On the other hand, medical institutions have concluded that Nimesulide-induced liver damage is statistically comparable to other NSAIDs, indicating that 5 out of 30 patients (17%) in their institutions had severe liver damage [23].
In 2009, our sequence included 42-43 recorded cases of Nimesulide-induced liver damage connected with a histological and broad clinical spectrum of hepatotoxicity [24-25]. To the best of our knowledge, this was the largest series of Nimesulide hepatotoxicity reports ever published. At the time of admission, the main symptoms examined were malaise (65%), jaundice (70%), and itching (50%). Interestingly, in 2/3 of patients, hepatotoxicity begins 15 to 90 days after taking the drug. Only 11% of them had a latency period related to drug safety of less than 15 days. On the other hand, normalisation exceeded 90 days in 27% of cases [26-28]. Serum alkaline phosphatase levels usually take longer to normalise than transaminases in cholestatic liver injury over a period of one year. [28] Nine patients in our observed series developed severe liver disease, and six cases were sufferers of fulminant hepatic failure as per the recently published data by Walker et al. [29]. This group of study consisted primarily of women aged 50 and more, out of which 2 patients died before the liver transplantation (the reason was multiple organ

failure), but a girl of an early age successfully underwent orthotopic liver transplantation. Consistent with her Bjarnason, who analysed 33 case reports, a wide range of variation was observed in ALT and aspartate transaminase levels, with 100% having at least a twice-fold increase [30].

In patients with confirmed hepatotoxicity from Nimesulide, extensive liver damage, including acute hepatitis and mixed, macro, and semi-large hepatic necrosis, has been observed. Hepatocellular necrosis was 64%, cholestatic hepatitis was 27%, and pure cholestasis was 9% [31, 32]. The mechanism of Nimesulide's hepatotoxicity has not been studied. It has been advocated that this may be due to the formation of reactive metabolites or the patient's genetic variations in drug metabolism [33]. Nimesulide was banned in India in 2011, while in other countries like the UK, Canada, New Zealand, Australia, and Denmark, it was banned in 2001, and in Singapore and Ireland, it was banned in 2007. The market for Nimesulide in India was around Rs 300 crore. Its sale was reduced after the Ministry of Health in India prohibited its use in children [34]. The Dr. Reddy's brand Nise was the largest-selling Nimesulide drug in India. As per the Drug Technical Advisory Board (DTAB), the other drugs are costly as compared to Nimesulide and therefore not affordable for poor people. A study says that COX-2 inhibitor celecoxib, available in the US, causes liver problems and Benzydamine, available in the UK, causes urticaria [35].

4. STATISTICAL ANALYSIS

Data has been computed from literature analysis. The mode used was bivariate followed by multivariate analysis to confirm the risk estimates for liver injury and drug utilisation were appropriately adjusted for confounders and effect modifiers [36]. Covariates included body mass index (BMI), smoking, alcohol, liver comorbidities such as gallstones, hepatitis, liver cirrhosis, nodules, and other hepatic diseases; heart comorbidities like stroke, arrhythmia, angina pectoris, heart failure, and cardiac surgery; and some adjacently prescribed drugs (Paracetamol, other NSAIDs, Amoxicillin, Macrolides, Amoxicillin/Clavulanic acid, antidepressants, and statins) [37]. There was BMI (less than one percent, in 11 of 1770), alcohol consumption (less than one percent, in 3 of 1770), and small missing data on smoking (all found in the control group, 1%, in 2 of 1770), Therefore, no method was used to account for missing data, and a full case analysis was performed [38]. Unconditional logistic regression was used to evaluate the effect of gender and age on the risk of liver injury in NSAID users. The sample size for the primary relative risk of Nimesulide-induced liver injury was estimated with a minimal risk of detection (OR) of 2.0, an alpha of 0.05, a grade of 80%, and a Nimesulide prevalence of 8%. Unconditional logistic regression was used to evaluate the effect of gender and age on the risk of liver injury in NSAID users [34]. Taking these assumptions into account, 163 cases and 1630 controls were required (case-control ratio of 1:10) [39]. Although the prevalence of the control group was slightly different (ranging between 5-10%), the sample size was considered adequate. This allows us to determine odds ratios in the range of 2.28 (alpha = 0.05, power = 80%). The latter proportion was found in the subjects of this study (184 Nimesulide users out of 1770 corresponding control subjects).

Table 2: Odds ratios and 95% confidence intervals for acute severe liver injury were related to different doses of Nimesulide

Drug Dose	No (%) of cases seen	No. (%) of controls	OR (95% CI)	ORAdg (95% CI)†
NIMESULIDE				
<200 mg	21 (11.73)	172 (9.72)	1.41 (0.85-2.35)	1.55 (0.89-2.70)
≥200 mg	9 (5.03)	12 (0.68)	8.03 (3.36-9.2)	10.69 (4.02-28.44)

OR- Odd ratio; CI- Confidence Interval

For the initial analysis, we focused on determining the risk for hepatotoxicity among patients who were treated with Nimesulide. We used the ORs or rate ratios reported in the cohort or case-control studies, respectively. If not reported, we calculated the ORs or rate ratios using the segment of patients reported with Nimesulide-induced liver injury in each study. The relation between the use of the drug and the hepatotoxicity risk was estimated using relative risks (RRs) and 95% confidence intervals (CIs). For spontaneous reporting databases, a coapprehensive disproportionate analysis was conducted by use of the

case/non-case method. Cases included all studies positive for hepatotoxicity, while non-cases included all the other reports analysed during the study. The relationship between hepatotoxicity and Nimesulide use was determined using the reporting odds ratio (ROR) as a measure of asymmetry. It is the ratio of the odds of Nimesulide exposure among cases to the odds of Nimesulide exposure among non-cases [40]. The authors collected raw data from the reports for all NSAIDs, counting Nimesulide, from studies to calculate the RORs, compared with other NSAIDs, and their corresponding 95% CIs. The meta-analysis counted the measures of risk as either RR or ROR. Sensitivity analysis determined possible heterogeneity between studies by including or excluding them from the meta-analysis, based on the study design and measure of the RR (i.e., OR and rate coefficient). The statistical heterogeneity of studies was assessed using the I2 statistics and Cochran's Q test. An I2 value of 50% or a P value of less than 0.10 in the Cochrane test indicates significant heterogeneity with respect to literature analysis. Overall RR estimates were obtained from random effects models in the presence of statistical heterogeneity. For the rest, a fixed-effects model was used, and SPSS version 23.0 (IBM SPSS Corp., Chicago, IL, USA) and comprehensive meta-analysis (Biostat, Englewood, NJ, USA) were used for data analysis [41-42].

5. DISCUSSION

In 2010, the Ministry of Health in Italy issued 'Law 38 to ensure access to sedative care andiroxicam and& pain treatment [3]. Nimesulide, the most commonly prescribed drug in Portugal and Italy, where Italy occupies half of the world market for this selective COX-2 inhibihas the drug. It has best gastro-intestinal endurance profile among all other commonly used, i.e. Piroxicam & Ketolalac recommending that 51 percent of all cases of acute liver failure can be ascribed to drugs, and various case reports express lethal hepatotoxicity in patients receiving NSAIDs. Era demonstrated that the occurrence of NIH in Italy was quiet low and not elevated with other NSAIDs. Although all of these data were gathered in Umbria, they do not represent all of the available cases in Italy.

The global incidence of NIL ranges from 1-9 cases per 100,000 survivors. Here, we present a complete analysis of the wide ranging series of Nimesulide-related hepatotoxicity. Our analysis highlights the capability of the Nimesulide to induce severe liver injury and active liver failure (ALF). NSAID hepatotoxicity has a higher prevalence in women. Secondly, there are potential conflicts with respect to the publications included in this review. Four of the 16 studies were fully funded by Nimesulide manufacturers [43]. In three studies, at least one of the authors was an employee of a Nimesulide manufacturer. Nine trials were published in symposium format in an issue of an industry-sponsored journal. But for new drugs, this seems inevitable when other independent sources are not willing to invest in such research. In some of the included studies, statements about funding sources can be examined to provide clarity. The long-lasting use of Nimesulide has not been evaluated. This is important because, in some cases, most of the Nimesulide-induced hepatotoxicity occurs after a comparatively long exposure period. Finally, the combined sample size may not be competent to compare rare side effects of the Nimesulide. Here we report a case of an elderly woman with induced hepatotoxicity in which liver transaminases improved significantly within days of drug discontinuation and returned to normal within seven days [43]. In this patient, In three studies, at least one of the authors was an employee of a Nimesulide manufacturer. Nine trials were published in symposium format in an issue of an industry-sponsored journal. But for new drugs, this seems inevitable when other independent sources are not willing to invest in such research. In some of the included studies, statements about funding sources can be examined to provide clarity. The long-lasting use of Nimesulide has not been evaluated. This is important because, in some cases, most of the Nimesulide-induced hepatotoxicity occurs after a comparatively long exposure period. Finally, the combined sample size may not be competent to compare rare side effects of the Nimesulide. Here we report a case of an elderly woman with induced hepatotoxicity in which liver transaminases improved significantly within days of drug discontinuation and returned to normal within seven days. After the first dose, the development of severe liver dysfunction was evidenced by a liver biopsy in the absence of other drugs or disease. Hence, this adverse event can be scrutinised as an idiosyncratic event exhibiting cholestasis or a hepatocellular pattern. The seriousness of these reactions ranges from asymptomatic advancement in liver function tests to case reports of acute liver failure leading to death-related conditions or the need for transplantation [44]. On the Naranjo

Probability Scale, the authors received a score of 6, indicating a possible link between patient hepatotoxicity and Nimesulide therapy. Literature revealed many reports of potential hepatotoxicity, and although the molecular mechanisms underlying the hepatotoxicity caused by this drug are not well understood, idiosyncratic reactions may be involved [45]. A possible mechanism of Nimesulide-induced hepatotoxicity may be associated with liver bioactivation. The drug does not form an acylglucuronide but is composed of an aromatic nitro group that undergoes nitro reductive activation and is associated with the toxicity of other Nitroaromatic compounds and aromatic amines. Notably, the hepatic bioactivation of Nimesulide generates reactive metabolites that can induce intracellular oxidative stress and mitochondrial damage [46]. Moreover, experimental studies have shown that incubation of mitochondria with Nimesulide activates and opens the mitochondrial permeability junction pore, resulting in depletion of enzymes such as adenosine triphosphate, osmotic swelling of the mitochondria, and the release of apoptosis-inducing mediators into the cytosol, which cause a wide spectrum of damage. All these procedures may have played a role in the overall mechanism of Nimesulide-induced hepatotoxicity in patients, and several studies have shown that hepatotoxicity is also caused by mixed injury and pure cholestasis [47].

Finland, followed by Spain and Ireland, reported the first cases of severe or fatal liver damage, causing drug discontinuation in 4,444 people in these countries. However, the most recent EMA review concluded that the benefit and risk profile remained favourable and limited use was recommended. These findings were supported by the several epidemiological studies, which confirmed that the Nimesulidewas related to a greater increase in risk. Our examined study supports this conclusion and provides more information on the exposure timing and dosage form. In several cases, Nimesulide was administered at the suggested exposure times and daily doses (duration less than 15 days and doses less than 200 mg) as mentioned in Table 2 [48].

Under all these conditions the risk associated with Nimesulide appears to be very low. Still, an exponential increase in the risk of hepatotoxicity is observed with long-term treatment duration and higher doses. In the patients, it is possible that the individual risk factors (such as increased production of certain reactive drug intermediates) or other epigenetic factors increased the risk of developing Nimesulide-related hepatotoxicity [49]. However, projecting NSAIDs in a negative light is not our motto; rather, it provides a comprehensive overview of the susceptibility of several major organs to nearly unavoidable drugs prevalent in everyday life. Research is needed to understand the different drug-related risk aspects of organ damage caused by NSAIDs. Many areas need to be studied from a mechanistic point of view, such as the connection between ROS and PG. Our study shows that Nimesulide use is associated with an approximately two-fold increased risk of hepatotoxicity [50]. A wealth of scientific data indicates that the drug should not be used as a first-line treatment as an antipyretic or analgesic. It is regrettable that the Indian government is waiting for another report from the committee before stopping the use of Nimesulide for the treatment of pain and fever, causing innocent patients to suffer needlessly. Several reports and reviews from drug regulatory authorities in Italy, Spain, and Ireland have warned about the adverse effects of Nimesulide on the liver. In Europe, the European Pharmacovigilance Database shows that this drug is associated with a number of severe cases of liver damage. Although the drug is banned in many countries such as Switzerland, Spain, Ireland, Finland, and the United States, it is still used as an over-the-counter drug in the Indian market without warning patients about the side effects and drug interactions [51].

6. CONCLUSION

From the above review, it is clear that NSAIDs are associated with 30% of hospitalisations with preventive side effects. Validated by a comprehensive dispro-portionate analysis showing an increased incidence of reported hepatic adverse events with Nimesulide compared to other NSAIDs in terms of absolute risk of toxicity. The cause of death was not thought to be related to liver damage. Age was a major causative parameter in hepatotoxicity. Careful monitoring for the development of liver failure is required. Patients in developing countries may not follow the required guidelines for simple economic reasons. Age, dosage, and underlying diseases are considered responsible for the hepatotoxicity of NNimesulide. Acute liver failure is observed in elderly and middle-aged patients between 2 and 3 weeks after starting drug treatment. There are also other combinations such as amoxillin and potassium clavulanate, which are banned in India, but no therapeutic explanation has been found for their use.

Moreover, Nimesulide is a well-tolerated anti-inflammatory and antipyretic agent that causes relatively few adverse drug reactions but is still recommended as not applicable as first-line treatment.

Conflict of interest

None declared

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