The Spectrum of Nimesulide-Induced-Hepatotoxicity. An Overview

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Abstract: Nimesulide is the unique molecule of the sulphonanilides class of non-steroidal antiinflammatory drugs [NSAIDs]: Nimesulide has analgesic, anti-pyretic, potent anti-inflammatory activities and very good gastro-intestinal [GI] tolerability. Therapeutic action is multifactorial, including cyclooxigenase-2 (COX-2) inhibition, scavenging of free radicals and inhibition of various pathways of inflammation. Nimesulide is oxidatively metabolised via liver cytochromes P450. Several unproven hepatotoxicy-predisposing-factors thought to be present in rheumatologic patients have been linked to a higher incidence of hepatic reactions in this sub-population. However, the molecular mechanism underlying hepatotoxicy remains to be elucidated. Nimesulide has been associated over two decades with reports of severe liver damage. The clinical presentation of nimesulide-related-hepatoxicity includes, malaise, pruritus, a wide range of ALT/AST elevation, and an average 4 fold elevation of alkaline phosphatase and GGT. Liver biopsy shows a predominance of hepatocellular involvement, less frequently cholestatic and mixed patterns. Both, the hepatitis pattern and the mixed-type combining cholestatic jaundice, might evolve into fulminant hepatic failure. However, the incidence of nimesulide-induced-hepatotoxicity is not homogeneous across the medical literature. Indeed, most of the countries find it to be comparable to that of other NSAIDs, while a significant higher hepatotoxicity is suggested by reports from Finland, Ireland and Argentina. Our series in Argentina comprising 43 cases is worrisome particularly because it evidences a significant proportion of severe forms. In the present work we analyze the epidemilogical characteristics of nimesulide-induced-hepatotoxicity and we describe the clinical and histologic spectrum of nimesulide-associated-liver damage based on the comparison of our series of 43 cases and worldwide published observations in the pertinent medical literature.

Keywords: Cholestasis, drug-induced liver injury, fulminant hepatic failure, hepatitis, hepatotoxicity.

1. INTRODUCTION

Nimesulide is an NSAID with analgesic, anti-inflammatory and anti-pyretic effects, due to potent inhibitory activity on the COX-2 enzymes. However, the mechanism of action is probably multifactorial, which has been largely attributed to a unique chemical structure of the sulphonanilides class of NSAIDs [1]. Following initial marketing in Italy in 1985, nimesulide is currently commercialized in over fifty countries. Our group in Argentina originated in 1997 the first observation ever reporting nimesulide-induced-hepatotoxicity. Indeed, at that point in time we were struck by the fact that in the few previous years we had dealt with 6 cases presenting with hepatocellular and cholestatic liver injury during nimesulide therapy for various conditions [2]. Our observation was confirmed by many case-reports or small series up to six patients each. In these, nimesulide was associated with a variety of patterns of liver reaction [i.e., hepatitis, cholestatic jaundice, and liver failure]. Importantly, a high proportion of reports exhibited severe clinical liver disease including fulminant hepatic failure [3-23]. As it is the case with other NSAIDs, drug-induced-hepatotoxicity is far less frequent [at least 10 times lower] than GI symptoms [which in turn take place in 1 out of 5 patients]. However, the continuous flow of reports, many of which showed severe forms of liver damage, while others documented liver involvement in association with extra-hepatic toxic manifestations [24-26] led the national health authorities of several countries to withdraw nimesulide from the market. Reports, mainly from Finland attracted the attention of the European Medicines Evaluation Agency [EMEA] –currently European Medicines Agency- as well as the Committee for Medicinal Products for Human Use. The evaluation carried out by these agencies found nimesulide-related-hepatotoxicity to be *no more frequent* than that of other NSAIDs. Thus, nimesulide commercialization was maintained in Europe, although the reports recommended a restricted length [15 days] and maximal dosage [100 mg per day] for nimesulide therapy [27]. In other words, we currently deal with two somehow confronting standpoints: the first one coming from clinical investigators concerned by reports linking nimesulide to severe hepatotoxicity, even in the absence of robust epidemiologic data; the other it that from health authorities who find nimesulide-induced-hepatotoxicity statistically comparable to that of the remainder NSAIDs.

This present work comprises: [I] A brief review intended for clinicians regarding pharmacokinetics of nimesulide, analyzing the mechanisms claimed to be responsible for ni-

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mesulide-induced-hepatotoxicity; [II] An overview of the clinical, biochemical and histological spectrum of nimesulide associated liver damage based on the current medical literature; [III] The presentation of our own series documenting 43 cases of nimesulide-induced-hepatotoxicity in comparison with data from the literature; [IV] Safety profile of nimesulide. The current stand point regarding the impact of severe nimesulide-induced-hepatotoxicity

2. THE CHEMICAL CHARACTERISTICS, PHARMACOKINETICS AND BIOLOGICAL ACTIVITY OF NIMESULIDE

Attending to chemical structure, there are 4 classes of NSAIDs. One out of these 4 is the Sulphonanilides Class. Nimesulide is a very unique chemical structure since it constitutes the single one compound of the Sulphonanilides Class of NSAIDs. The name of the drug given by inventor G. Moore stands for 4-nitro2-phenoximethane-sulphonanilide [28] and took place in 1974 preceding the discovery of cyclooxygenase, and also before current awareness regarding the role of prostaglandins in inflammation and pain. The background information at that point suggested targeting free radicals, considered key factors for inflammation. Accordingly, the rationale was to design a drug capable of scavenging the free radicals excess [29,30].

Nimesulide is readily absorbed reaching a peak plasma concentration 1 to 3 hours after oral intake. This enables a rapid onset of analgesic, anti-inflammatory and anti-pyretic effects [31]. Nimesulide undergoes oxidative hepatic metabolism by cytochromes P-450 [CYP-2C9, CYP2C19, CYP1A2] to an active -albeit less potent- 4-hydroxi-metabolite [32]. In spite of a strong binding to plasmatic proteins, nimesulide is readily distributed in the synovial fluid, a crucial feature accounting for therapeutic effectiveness in joint disease. Nimesulide half life ranges from 2 to 5 hours and that of active 4-hydroxi-metabolite ranges from 3 to 9 hours. No drug interactions between nimesulide and classical cytochrome inhibitors, such as cimetidine, warfarin, acenocoumarol, hypoglycemics agents, digoxin, furosemide, has been found to be clinically relevant [31,32].

The mechanism of action of nimesulide is multifactorial. Indeed, it exerts its therapeutic action through a combination of effects on various biological pathways [33,34]. Inhibition of inflammation results from potent inhibitory activity on the COX-2 production of prostaglandin E2 [PGE2] [35]. Nimesulide action is also related to inhibition of histamine release from astrocytes, mast cells and basophils, scavenging of free radicals [hydroxyl radicals], hypochlorous acid production, inhibition of neutrophil adherence, inhibition of PAF from activated platelets, inhibition of metalloproteinases, and reduction of metalloproteinases release, reduction of apoptotic chondrocytes, inhibition of nitric oxide synthase (NOS) with reduction in NO production; thus acting on oxygen reactive species, the key mediators of cell death, and the inflammatory process [36]. In addition, nimesulide shares with other NSAIDs an effect on glucocorticoid receptors through which an increase in the activity of endogenous glucocorticoidsteroids is achieved [37,38].

3. NIMESULIDE ASSOCIATED LIVER DAMAGE

Hepatotoxicity associated with NSAIDs has been judged as an infrequent phenomenon [39-42]. Regarding the severity of liver involvement, a wide spectrum of situations has been reported, ranging from mild ALT/AST elevation to severe forms including fulminant liver failure. Biochemical and histologic characterization discloses a predominance of hepatocellular injury, over cholestatic and mixed patterns. The mechanism of hepatotoxicity of NSAIDs is idiosyncratic and unpredictable with the exception of paracetamol, the hepatotoxicity of which -regrettably well known by transplant hepatologysts- is a dose-dependant predictible liver injury [43-45]. Most of the information currently available related to NSAIDs toxicity of is derived from *in vitro* and *in vivo* studies mainly on paracetamol and diclofenac. Specifically for the case nimesulide, it has been postulated that hepatotoxicity could be due to the excessive formation of a reactive metabolite. This hypothesis attributes the reactive metabolite formation to genetically determined variants in hosts metabolic pathways or to the concomitant use of other medications [*vide infra*] [46,47]. Still unproven hepatotoxicy-predisposing-factors thought to be present in rheumatologic patients have also been linked to a higher incidence of hepatic reactions in the nimesulide sub-population, in a way that could compare with the aspirin-induced acute and chronic hepatitis cases seen in hypoalbuminemic SLE patients [48,49]. Likewise, experimental studies have demonstrated an increased salicylate hepatotoxicity in rats after induction of rheumatoid arthritis [50]. However, the precise molecular mechanism underlying NSAID hepatotoxicity remains to be elucidated.

The possibility that nimesulide-hepatotoxicity develops as the result of concomitant medications is particularly relevant since the drug is frequently associated in clinical practice with a variety of antibiotics, This is a two-ways association: antibiotics added in febrile patients already taking nimesulide for a given baseline condition, as well as proven bacterial infections in which nimesulide is added to antibiotic therapy to reduce inflammation. Among these we should be reminded about the hepatotoxic potential of amoxicillin-clavulanic responsible for idiosyncratic cholestatic hepatotoxicity [51]. Concomitant medication is a major issue regarding the adjudication of nimesulide-hepatotoxicity. Indeed a long list of simultaneously prescribed drugs affects many of the reported cases causing interference in the process of calculation and statistics on nimesulide hepatotoxicity [47, 51].

Nimesulide toxicity at the cellular level is as yet unclear. Intracellular reactions affecting mitochondrial physiology and generation of apoptosis has been described. At the molecular level the reductive bio-activation of the nitro aromatic group of nimesulide induces oxidative stress and might result in covalent binding of active metabolites to cellular proteins [52]. Supra-therapeutic doses of nimesulide uncouple oxidative-phosphorilation and increase cellular membrane permeability [47]. The postulated deleterious reactive metabolites of nimesulide have not yet been demonstrated in cell culture. Human cell culture coincubation of nimesulide with antibiotics, hormones and a variety of hepatotoxic drugs failed to disclose significant drug interactions [53].

3.1. The Risk of Nimesulide-Induced-Hepatotoxicity

According to a recent study hepatic steatosis and the metabolic syndrome might predispose to nimesulide -and other NSAIDs hepatotoxicity [53], a situation similar to that already proven for methotrexate and halothane [54-56].

Nimesulide at a concentration of 30 to 50 mmol/L caused an increase in mitochondrial oxygen consumption in an *ex vivo* isolated liver perfusion setting of adjuvant-induced-arthritic-rats. Inhibition of gluconeogenesis and stimulation of glucogenolysis took place as well. Since the mitochondrial effect is dependant on the arthritis condition of the experimental animals, these findings suggest a special susceptibility to nimesulide-induced-mitochondrial-damage in arthritic conditions [57].

It has already been emphasized that in the clinical setting the possibility of documenting the causative role of a drug in the individual patient is not at all an easy task. The clinician needs to critically evaluate the possibility that other factors play a role in the actual findings. Particularly alcohol or other substance or drug use, as well as preexisting conditions might participate in the laboratory or histologic changes [58]. In the 1990s some models were developed aimed at drug-causality-assessment. These are scores based on a number of variables, each of them presented in the form of a numeric scale weighing evidence to attain a clinical diagnosis of drug-induced hepatotoxicity. Prospective validation of these scores has led to the conclusion that they constitute valid tools to reliably assess drug-induced liver disorders [59-62]. The second important difficulty is the lack of a convincing perspective regarding the dimensions of drug hepatotoxicty. Indeed no solid epidemiological information is available. No prospective studies have been undertaken to sample the actual incidence of hepatic reactions in the exposed population. This applies not only to nimesulide and the other massively consumed NSAIDs but to the vast majority of marketed products. Massive consumed products add uncertainties regarding the exposed population [i.e., the absence of a reliable denominator]. On the other hand despite the broad spectrum of drug-induced-hepatotoxicity described for nimesulide and the other NSAIDs, these drugs are associated with a low frequency of severe liver damage [63-65]. The estimated incidence is 1 to 5 cases per 100.000 exposed individuals [8,66-68]. The specific case of nimesulide is contradictory. On one hand some published evidence points out a higher degree of hepatotoxicity for nimesulide [53,63] while others have failed to demonstrate any difference between nimesulide and the remainder NSAIDs regarding the incidence of liver reactions [69-72].

A cohort study by Traversa [73] involving 400.000 patients receiving NSAIDs concluded that nimesulide is associated with minimal risk of hepatotoxicity. *Age* was the unique identified feature causing an increase in liver damage [74]. The same group retrospectively analyzed all prescriptions of NSAIDs issued in a central Italy region from 1997 through 2001 documenting cases of hepatotoxicity. A 1.4 fold increase [95% CI, 1.0-2.1] of hepatotoxicity was disclosed when compared with historic findings. This study did not document severe liver damage caused by nimesulide.

Notwithstanding, the risk of liver toxicity by nimesulide appeared to be higher than that of other NSAIDs. The limiting factor imposed by the methodology which prevented drawing further conclusions relied in the fact that data proceeded directly from a database of prescriptions devoid of dosage specification or clinical information on recipients. The overall result is in keeping with a previous canadian cohort study [39] involving 1.500.000 prescriptions which reported an incidence of hepatotoxicity of 9 per 100.000 person/years [95% CI: 6-15].

Despite the proliferation of reports describing severe forms of nimesulide induced-hepatotoxicity the epidemiological studies have almost unanimously concluded that severe liver damage is of low frequency incidence determining a positive risk-benefit-ratio. This same concept was confirmed by the Consensus Report Group on Nimesulide held in Rome on 2005 [38] after a critical review and comprehensive analysis of published information concerning chemistry, pharmacokinetics of nimesulide, its safety profile as well as clinical reports on nimesulide-related-hepatotoxicity. Thus, nimesulide was confirmed to be a potent and rapidly acting NSAID, associated with a better GI tolerance than other NSAIDs and similar hepatotoxicity [38].

Rigorous data collecting, caution and clinical commitment are required when judging potential hepatotoxicity, particularly in the consideration of two variables: *latency* to toxic evidence and *normalization* after drug withdrawal. Indeed, pharmacovigilance chronologic criteria should be fulfilled in order to adjudicate responsibility of a given effect to the action of a drug. It is always conflicting the situation in which a hepatotoxicity picture develops late [time after the intake of the drug has been already discontinued].

Specifically concerning nimesulide hepatotoxicity there are reports that did not meet the chronologic criteria currently recommended, which eventually led to erroneously adjudicate severe hepatic illness and fulminant hepatic failure with insufficient documentation [74,75]. In other words overdiagnosis of nimesulide-induced-hepatotoxicity is another likely source of error when judging the spectrum of hepatic reactions.

4. CLINICAL CHARACTERISTICS OF NIMESULIDE AND NSAIDS HEPATOTOXICITY

Hepatotoxicity associated with NSAIDs, comprises a wide spectrum of clinical, biochemical and histologic manifestations. Liver involvement is usually acute and predominantly necroinflammatory. Biochemical and histologic characterization discloses a predominance of hepatocellular injury, over cholestatic and mixed patterns. Not infrequently asymptomatic mild ALT/AST elevation is documented during NSAIDs treatment. This has been reported to be as high as 15%, with a majority of cases showing that LFTs return to baseline values despite the continuity of NSAIDs treatment [54,76,77].

Quite a similar pattern applies to nimesulide-induced-hepatotoxicity. Our original report [2] and those which followed documented hepatocellular, cholestatic liver injury or a mix of both during nimesulide therapy. Importantly, according to reported cases, both, the hepatitis pattern and the mixed-type combining cholestatic jaundice, associated a high proportion of severe clinical liver disease and liver fail-

ure including fulminant hepatic failure. A very important paper in this latter aspect was that of P.A. McCormic in 1999 [78], which prompted several official reactions and led the national health authorities of several countries to withdraw nimesulide from their national markets [79-83].

Regarding the argentine experience with nimesulide-hepatotoxicity, the 2 first cases were seen on 1988, - 2 years after commercialization started in the country- both were females, receiving the drug for osteoarthritis, at a daily dose of 200 mg of nimesulide. The first one, a 66 y/o (years-old) developed pruritus and severe jaundice after 2 weeks of therapy. The liver biopsy showed cholestatic hepatitis with portal and lobular lymphocytic infiltration and severe canalicular cholestasis Fig. (**1**). The second case was 83 y/o, presented with pruritus and anicteric cholestasis, which led to nimesulide withdrawal. The most interesting point is that a self-decided [i.e., non-iatrogenic] new intake of nimesulide resulted in reappearance of pruritus 4 days later, confirmed in its nature by the increase in alkaline phosphatase, GGT and ALT, shaping an involuntary drug rechallenge.

Fig. (1). Hepatocellular and cholestatic injury in a 66 y/o woman who presented intense itching as the main clinical symptom. [Hepatocellular bilirrubin stasis (white arrow) and lobular inflammation (black arrow)].

On 2001, mainly due to referrals after our initial communication in 1997, our database totalized 30 cases, out of which 17 % had severe liver injury or fulminant hepatic failure [84]. In 2009, which is to say 23 years after nimesulide was marketed in Argentina, our series includes 43 documented cases [unpublished data] of nimesulide-induced-hepatotoxicity. To our knowledge this constitutes the largest series of nimesulide hepatotoxicity.

When confronted with a scoring system to assess causality of adverse reaction to drugs, all our cases fall into the *possible* or *probable* categories. We adopted restrictive criteria, and we did not include patients with dubious clinical features and multifactorial disease, we excluded those with concomitant medications, namely: amoxicillin clavulanate, diclofenac, tuberculostatic agents, herb medication, diphenilhidantoine, as well as those with alcohol abuse. An additional exclusion was that of cases with any other concomitant medication in which *latency* made it possible to face get a confounding interference in the diagnosis of nimesulide-induced-hepatotoxicity. Presence of hepatotropic viruses, other etiological factors for liver disease and abdominal US were assessed in all cases. This large series would indicate a higher incidence of nimesulide hepatotoxicty in Argentina. However, there are alternative explanations, for instance Rainsford postulated that locally manufactured preparations could contain impurities [unpublished data]. The impurities hypothesis [according to Rainsford] would also apply to Uruguay, [the neighbor country of Argentina] where nimesulide has been withdrawn from the market due to several cases of fulminant hepatic failure followed by death [3]. Data from Finland showed an increase in liver toxicity when compared with the rate of adverse events affecting other systems [i.e., dermatologic, renal, GI] [85,86]. The observation led the National Agency for Medicine of Finland to draw nimesulide out of the national market [82]. However, a further review of potential explanations for nimesulide toxicity in Finland, 2001-2002 disclosed interesting environmental and genetic cofactors. Severe hepatotoxicity was frequently associated with alcohol abuse, concomitant medications - estrogen, statins, paracetamol and diclofenac- [87,88]. In other words, the possibility of comorbidities or drug interaction was raised. Furthermore, a surprisingly high incidence of cholestasis of pregnancy as well as estrogen-related-liver-disease in conjunction with hepatic lipase abnormalities [89,90] with the potential of altering statin metabolism were also considered as cofactors for nimesulide-related-liver-reactions reported in Finland [82].

4.1. The Bjarnason Series and the Argentine Series

On 2005, Bjarnason presented a series of 41 cases of nimesulide-hepatotoxicity, a selection of well documented reports devoid of confounding factors. Female predominance [30:11], mean age: 56.5 y/o, range: 17-83, 40% older than 65. [52]. The argentine series shows a comparable population [unpublished data]: female predominance [35:8], mean age: 59.9 y/o, range: 9-82, 30% older than 65. The daily dosage 200 mg in 42 out of 43 cases and 400 mg in one out of 43 cases. The most common symptoms at presentation were jaundice in 70%, malaise in 65% and pruritus in 50% Fig. (**2**). Upper abdominal pain was present in only 16%, which is lower than the literature reports. Only one out of 43 patients was asymptomatic. In this case hepatotoxicity was incidentally detected through LFTs alteration [i.e., a 2 fold elevation of ALT/AST, and 4 fold elevation of alkaline phosphatase and GGT] on a routine laboratory test. The range of *latency* [defined as the span between the initiation of nimesulide therapy and the development of clinical/biochemical evidence of hepatotoxicity] varies widely from 4 to 210 days. Fig. (**3**). Latency was found to be shorter among males [35 days, range: 4-60] than females [60 days, range 10-210]. In 37% of cases latency was shorter than 30 days and in 23% longer than 90 days. Relevant to drug safety in only 11% latency was shorter than 15 days. Therapies shorter than 15 days are significantly safer than longer therapies. Finally, relevant to diagnosis and clinical suspicion we should bear in mind that 11% of our patients had a latency span extended for more than 5 months. On the other hand normalization of LFTs averaged 66 days, [range: 15 – 240]. Normalization

exceeded 90 days in 27% of cases. Fig. (**4**). It is well known that normalization of cholestasis takes significantly longer than normalization of transaminases [2,8]. Accordingly, 7 out of 7 cases with high serum concentration of alkaline phosphatase, all normalized this test exceeding 4 months.

Fig. (2).

Mean +Standard Deviation: 56±55 days
(Median: 35days, range: 4 –210)

Fig. (3). Further breaking of these results show that *latency* shorter than 15 days in occurred in 11%. Therapies shorter than 15 days are significantly safer than longer therapies. On the opposite end and relevant to clinical suspicion and diagnosis: other 11% of patients had an extended *latency span* (i.e., >5 months).

Mean +Standard Deviation: 66 +53 days
(Median: 60days, range: 15 –240days)

Fig. (4).

Six patients [14%] developed fulminant hepatic failure, five of which developed ascites **(**Table **1**). In agreement with the recent publication by Walker and co-workers [91] this subpopulation was composed predominantly by females older than 50 y/o. The outcome was normalization in 3 out of 6 cases, despite the fact that one patient died due to cerebral vascular accident shortly after hepatic recovery. On the other hand, a 9 y/o girl required OLT (orthotopic liver transplantation) which was successful (Fig. **5**), the remainder 2 patients died before OLT due to liver and multiorgan failure. Pathological examination was available in 4 cases, two showed massive hepatic necrosis, one had sub-massive hepatic necrosis, and one had massive coagulative hepatic necrosis associated with macro and microsteatosis. This latter case is illustrative of preexisting liver disease aggravated by nimesulide: This patient had autoimmune hepatitis, which had been stable after ten years on combination therapy [prednisone plus azathioprine] with normal LFTs in previous controls, she developed rapidly evolving liver failure after receiving nimesulide for 40 days Fig. (**6**).

4.2. Biochemical and Pathologic Evidence of Liver Injury

Regarding ALT/AST elevation due to nimesulide hepatotoxicity a wide range of variation is the rule. Bjarnason ana-

Table 1. Nimesulide-Induced Fulminant Hepatic Failure in 6 Patients

Pts	Sex	Age	Latency (Days)	Recovery Time (Days)	Outcome and Comments
1	F	65	60	60	Died [Stroke after FHF recovery]
2	F	66	40	-	Died [AIH treated with prednisone/azatioprine]
3	F	32	90	-	Died
4	F	73	60	90	Alive
5	M	56	20	60	Alive
6	F	9	30	-	Alive – OLT

lyzed 33 case-reports observing that an elevation of ALT of at least 2-fold was present in 100%, and a 5-fold elevation in 89% [52]. In our series in Argentina we echoed this finding: ALT ranged from 58 to 4130 IU/L and AST from 36 to 4650 IU/L (Table **2**). Interestingly in 28% of cases AST was higher than ALT, a relation known to be indicative of extensive hepatocellular injury such as that of *massive hepatic necrosis*. However this was not the case in our series. Some patients showing AST predominance had only mild hepatocellular necrosis. Eleven percent of patients showed peripheral eosinophilia, only 2 of which had a tissue counterpart of eosinophils in liver biopsy.

Fig. (5). Massive panlobular hepatic necrosis (see black arrow) in a 9 y/o girl who received nimesulide for fifteen days before to the onset of clinical symptoms. She is alive after successful ortotopic liver transplantation

Fig. (6). 66 y/o female patient on corticosteroids and azathioprin for autoimmune hepatitis who developed rapidly-evolving *massive hepatic necrosis* associated with macro and microsteatosis and cholestasis. (Canalicular bile plug – lack arrow)

Liver histology comprises a variety of lesions induced by NSAIDs including acute hepatitis, chronic hepatitis, cholestasis, mixed forms, granuloma, steatosis, massive hepatic necrosis. However, when the spectrum of liver lesions is restricted to nimesulide-induced-hepatotoxicity, granulomata and steatosis have never been described. Regarding the predominant histologic pattern Bjarnason reports hepatocellular necrosis in 65%, cholestatic hepatitis in 25%, and pure cholestasis in 10 %. The argentine series shows identical results (Table **3**): hepatocellular necrosis in 64%, cholestatic hepatitis in 27% and pure cholestasis in 9 % Fig. (**7**).

Microvesicular steatosis was described in two cases. One of them associated with portal inflammatory infiltrate, lobular extinction and collapse with eosinophilic infiltrate Fig. (**8**). He underwent portal pressure measurement through a transjugular approach and the Hepatic Venous Pressure Gradient [HVPG] showed subclinical portal hypertension: 8.3 mmHg. The corresponding liver biopsy comprised 14 portal tracts, none of which showed portal fibrosis or regenerative nodules. The other case was observed in a 44 y/o female patient on corticosteroids and azathioprin for Autoimmune Hepatitis who developed rapidly-evolving *massive hepatic necrosis* Fig. (**6**).

5. SAFETY PROFILE OF NIMESULIDE. THE CURRENT STANDPOINT REGARDING THE IMPACT OF SEVERE NIMESULIDE-INDUCED-HEPATOTOXICITY

Nimesulide is better tolerated than most other NSAIDs. Furthermore a significant lower incidence of gastroduodenal ulcers, and GI perforation has been established [52,53,93]. A multicentric trial aimed at assessing NSAIDs-related-upper-GI-bleeding documented significant less bleeding imputable to nimesulide than that related to piroxicam, ketorolac and ketoprofen. The risk of GI complication by nimesulide was the lowest and was comparable to that of ibuprofen [94].

Efficacy and safety of NSAIDs for individuals bearing osteoarthritis and rheumatoid arthritis has been subjected to meta-analysis [92] comprising 19 trials, published from 1990 through 2001, including 2925 cases. The overall incidence of adverse events was 29% for naproxen, 20% for diclofenac and nimesulide and 10% meloxicam, irrespective of severity. A marked disparity is evident when comparing reports from Finland and Israel [68% and 69% of adverse events] with those from Turkey and Italy [6% of adverse events in both cases].

On 2005 EMEA, issued a recommendation of restricting nimesulide usage to short term therapies based on the fact that in most cases a latency of at least 15 days was found [95]. It was judged that therapies shorter than 15 days were significantly safer. However, on 2007, Helsiin Healthcare issued a report stating the positive safety profile of nimesulide based on an estimation of 500 million users along 22 years in the market [Press Report, Helsiin Healthcare, 17th May 2007].

Nimesulide continues to be marketed on over 50 countries [96]. It was never approved in the USA, Canada, England, Japan, Australia and New Zealand. On 2009 Argentina banned nimesulide commercialization based on its link to severe hepatotoxicity adding its name to the list of countries which at different points in time withdrew nimesulide from their market for similar reasons: Finland, Spain, Ireland, Por-

Table 2. Liver Function Tests [LFTs] in 43 Patients with Nimesulide-Induced Hepatotoxicity

VARIABLE	x ± SD	Range	Median	Normal Values
ALT	563 ± 733	58 – 4130	365	≤ 22 Ul/L
AST	532 ± 926	36 – 4650	240	≤ 18 Ul/L
ALP	397 ± 341	67 – 1348	270	≤ 48 Ul/L
GGT	184 ± 148	20 – 624	130	≤ 28 Ul/L
Total Bilirubin	14.1 ± 14.9	0.8 - 57	9.4	≤ 1.2 mg/dl

Table 3. Pathological Characteristics in Eleven Patients with Nimesulide-Related Liver Damage

Pts	Age	Sex	Hepatocellular	Colestatic	Mixed	Steatosis	Eosinophilia	Figure
1	66	F			X			1
2	62	F			X		X	
3	48	M			X			
4	32	F		X				7
5	32	F	MassiveNecrosis					
6	52	M	LobularCollapse			X	X	8
7	56	F	SubmassiveNecrosis					
8	56	F	LobularCollapse					
9	73	F	MassiveNecrosis					
10	66	F	MassiveNecrosis			X		6
11	9	F	MassiveNecrosis					5

with a latency of 4 to 60 days, all of which died in liver failure.

Fig. (7). Pure hepatocanalicular cholestasis induced by nimesulide (Canalicular bile plug- see black arrow)

tugal, Uruguay and Singapur. The decision in Argentina was based on the already alluded reports [8,82,84,91] and the most recent communication by Mendoza on 2007 [97] adding 3 new cases of fulminant hepatic failure, documented in female patients older than 50 y/o, treated for osteoarthritis

Fig. (8). Acute hepatitis induced by nimesulide with steatosis and extensive areas of hepatocellular collapse.

Nimesulide was associated with hepatotoxicity in the pediatric population for the first time in Portugal 1992,

where 2 cases of Reye syndrome were attributed to nimesulide This country suspended nimesulide commercialization shortly after this report [98]. A similar situation took place in India as a consequence of several claims, finally Indian authorities suspended nimesulide use in pediatrics adding the recommendation of its replacement by ibuprofen or paracetamol [99-102]. Venezuela underwent the same process on 2005 banning from the market all products containing nimesulide for pediatric indication [103]. Interestingly, the risk of nimesulide-induced-hepatotoxicity appears to be lower in the pediatric population compared with the general adult population. According to a critical review there is no demonstration of increased risk of nimesulide in pediatric population when prescribed for short therapies [104]. However in order to avoid any minimal risk, strong recommendations for the exclusive use of paracetamol and ibuprofen have been issued [105, 106].

In other words, we currently deal with two somehow confronting standpoints: the first one coming from clinical investigators concerned by reports linking nimesulide to severe hepatotoxicity, even in the absence of robust epidemiologic reference; the other it that from health organizations who find nimesulide-induced-hepatotoxicity statistically comparable to that of the remainder NSAIDs. Indeed, despite the proliferation of reports describing nimesulide induced-hepatotoxicity the epidemiological studies have almost unanimously concluded that severe liver damage is of low frequency incidence determining a positive risk-benefit-ratio. Some countries never approved nimesulide other withdrew it from market [107].

It has already been emphasized that in the clinical setting the possibility of documenting the causative role of a drug in the individual patient is not an easy task. The clinician needs to critically evaluate the possibility that other factors play a role in the actual findings. Overdiagnosis of nimesulide-induced-hepatotoxicity is a likely source of error when judging the spectrum of hepatic reactions. As such it should be avoided. Rigorous data collecting, caution and clinical commitment are required when judging potential hepatotoxicity. We as clinicians have learnt this lesson and a specific question regarding nimesulide intake has been incorporated to standard anamnesis.

CONCLUSIONS

Nimesulide exhibits a very good GI tolerance, and lower frequency of GI adverse events than the other NSAIDs. This is attributed to antioxidant, antisecretory, antihistaminic effect, and leukocyte inhibition. Regarding nimesulide- induced –hepatotoxicity:

Nimesulide has been associated over two decades with liver damage including a variety of patterns: hepatitis, cholestasis, mixed forms and *liver failure*. Incidence of *severe* hepatotoxicity is worrisome because several countries (Finland, Ireland and Argentina) have reported a large proportion of cases with severe nimesulide hepatotoxicity.

Cofactors such as underlying unnoticed liver disease, exposure to alcohol or other environmental factors, impurities in manufacture, genetically determined diathesis for hepatotoxicity, have been postulated to explain these effects. Likewise, several unproven hepatotoxicity-predisposing-factors thought to be present in rheumatologic patients have been linked to a higher incidence of hepatic reactions. However, the molecular mechanism underlying hepatotoxicy remains to be elucidated.

On the other hand, no solid epidemiological information is available. No prospective studies have been undertaken to sample the actual incidence of hepatic reactions in the exposed population. For massively consumed products there are uncertainties regarding the exposed population [i.e., the absence of a reliable denominator] even overdiagnosis of hepatotoxicity seems to play some role. The evaluation carried out by the European Medicines Agency- as well as the Committee for Medicinal Products for Human Use found nimesulide-related-hepatotoxicity to be *no more frequent* than that of other NSAIDs.

Nevertheless, the national health authorities of several countries have withdrawn nimesulide from the market. Others never approved it. Even favourable reports currently recommend a restricted length [15 days] and maximal dosage [100 mg per day] for nimesulide therapy, which in addition should be avoided in children. Undoubtfully, the past history of nimesulide intake needs to be specifically targeted and ruled out by rigorous anamnesis of patients bearing liver disease.

ABBREVIATION LIST

NSAIDs	=	Non-steroidal antiinflammatory drugs
DILI	=	Drugs Induced Liver Injury
GI	=	Gastro-Intestinal
y/o	=	Years-old
COX-2	=	Cyclooxigenase-2
EMEA	=	European Medicines Evaluation Agency
NOS	=	Nitric oxide synthase
PGE2	=	Prostaglandin E2
PAF	=	Platelet-activating factor
LFTs	=	Liver Function Tests
HVPG	=	Hepatic Venous Pressure Gradient
OLT	=	Orthotopic Liver Transplantation

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