Nimesulide-induced Hepatitis and Acute Liver Failure

Peretz Weiss MD[1], Meir Mouallem MD[2], Rafael Bruck MD[3], David Hassin MD[4], Amir Tanay MD[5], Chaim M. Brickman MD[5], Zvi Farfel MD[2] and Simon Bar-Meir MD[1]

[1]Liver Service, Department of Gastroenterology and [2]Department of Internal Medicine E, Sheba Medical Center, Tel-Hashomer, and Departments of [3]Gastroenterology and [5]Rheumatology, Wolfson Medical Center, Holon [Affiliated to Sackler Faculty of Medicine, Tel Aviv University], and [4]Department of Internal Medicine C, Hillel Yaffe Medical Center, Hadera, Israel

Key words: nimesulide, hepatitis, acute liver failure, drug-induced liver disease

Abstract

Background: Nimesulide is a relatively new nonsteroidal anti-inflammatory drug that is gaining popularity in many countries because it is a selective cyclooxygenase 2 inhibitor. Occasionally, treatment is associated with mild elevation of liver enzymes, which return to normal upon discontinuation of the drug. Several cases of nimesulide-induced symptomatic hepatitis were also recently reported, but these patients all recovered.

Objectives: To report the characteristics of liver injury induced by nimesulide.

Patients and Methods: We report retrospectively six patients, five of them females with a median age of 59 years, whose aminotransferase levels rose after they took nimesulide for joint pains. In all patients nimesulide was discontinued, laboratory tests for viral and autoimmune causes of hepatitis were performed, and sufficient follow-up was available.

Results: One patient remained asymptomatic. Four patients presented with symptoms, including fatigue, nausea and vomiting, which had developed several weeks after they began taking nimesulide (median 10 weeks, range 2–13). Hepatocellular injury was observed with median peak serum alanine aminotransferase 15 times the upper limit of normal (range 4–35), reversing to normal 2–4 months after discontinuation of the drug. The remaining patient developed symptoms, but continued taking the drug for another 2 weeks. She subsequently developed acute hepatic failure with encephalopathy and hepatorenal syndrome and died 6 weeks after hospitalization. In none of the cases did serological tests for hepatitis A, B and C, Epstein-Barr virus and cytomegalovirus, as well as autoimmune hepatitis reveal findings.

Conclusions: Nimesulide may cause liver damage. The clinical presentation may vary from abnormal liver enzyme levels with no symptoms, to fatal hepatic failure. Therefore, monitoring liver enzymes after initiating therapy with nimesulide seems prudent.

IMAJ 1999;1:89–91

See Editorial on page 98

Nimesulide (4-nitro-2-phenoxy-methane-sulphonanilide, Helsinn Healthcare SA, Switzerland) is a relatively new nonsteroidal anti-inflammatory drug that has both antipyretic and analgesic properties [1]. Its use is rapidly increasing in many countries mainly because it is a relatively selective cyclooxygenase 2 inhibitor [2]. In clinical trials the drug exhibited adverse effects similar to those of other NSAIDs: gastrointestinal disturbances, skin reactions, and effects on the central nervous system [1,3,4]. Hepatic injury has also been reported, manifested as mild elevations of serum aminotransferase that returned to normal when medication was discontinued [1,5]. Recently, several patients with nimesulide-induced symptomatic hepatitis and jaundice have been reported, all of whom recovered completely [6].

We describe six patients with nimesulide-induced liver damage, four with overt symptomatic hepatitis, and one with fatal acute hepatic failure.

Case Reports

Case 1

A 61-year-old man was treated with diclofenac and misoprostol for osteoarthritis of the cervical spine. Eight months later the two drugs were discontinued, and nimesulide 100 mg bid was begun. During the entire period the patient had also been taking omeprazole 20 mg every other day for heartburn.

Routine blood tests obtained 2 months after initiation of nimesulide revealed serum levels of alanine aminotransferase 375 U/L (normal 9–45) and aspartate aminotransferase 273 U/L (normal 8–40). Alkaline phosphatase and bilirubin levels, routine blood tests and ultrasonogram were normal. Serological tests for hepatitis A, B and C, Epstein-Barr virus and cytomegalovirus as well as for autoantibodies against nuclear and smooth muscle revealed no findings. Nimesulide and omeprazole were discontinued, and serum aminotransferase levels returned to normal. Omeprazole was then restarted and liver enzymes have remained normal.

Case 2

A 62-year-old woman was taking nimesulide 100 mg bid for low back pain. Three weeks later, while still on nimesulide, she complained of fatigue, anorexia and nausea,

which worsened during the following week. Her blood tests at that time revealed ALT 708 U/L, AST 546 U/L and γ-glutamyl transepeptidase 122 U/L (normal 8–78). ALP, bilirubin and other routine blood tests were within normal limits. Serological tests for viral and autoimmune hepatitis were negative. Of note, her liver enzyme tests were consistently normal on many previous visits to the clinic. Nimesulide was discontinued and within 5 days her symptoms had disappeared. The next week ALT was 513 U/L, and 8 weeks later returned to normal levels.

Case 3

A 41-year-old woman had been suffering for 18 months from polyarthritis involving the wrists, metacarpophalangeal and proximal interphalangeal joints. Repeated liver enzyme tests in the past had been normal. She was prescribed nimesulide 100 mg bid which she took for 4 months with partial clinical response. At that time she developed nausea, and blood tests revealed ALT 643 U/L and AST 359 U/L. However, ALP, bilirubin and other routine tests were within normal limits. Serological tests for viral and autoimmune hepatitis were negative, and abdominal ultrasonography demonstrated a normal liver and spleen. Nimesulide was discontinued.

A week later, ALT and AST levels were 800 and 412 U/L, respectively. Five weeks later they decreased to 123 and 69 U/L, and 3 months later were normal.

Case 4

A 70-year-old woman, known for years to have osteoarthritis and fibromyalgia but normal liver function tests, was prescribed nimesulide 100 mg twice daily together with 40 mg famotidine. Thirteen days later she presented with weakness and vomiting. Laboratory tests revealed ALT 169 U/L, AST 165 U/L and ALP 1,243 U/L (normal 82–290). Her serum bilirubin was normal, and serological tests for viral hepatitis and autoantibodies were negative. An abdominal ultrasonogram showed a homogeneous and slightly enlarged liver. Medications were discontinued. Two weeks later her symptoms subsided and serum aminotransferase levels returned to normal, but serum ALP was still 536 U/L. ALP was normal when tested 2 months later.

Case 5

An 18-year-old girl with systemic lupus erythematous of several years duration had been treated with hydroxychloroquine 200 mg and prednisone ≤10 mg or less daily. Her liver function tests were normal. During a flare-up of musculoskeletal pain she received nimesulide 200 mg per day.

After 11 weeks she began to complain of fatigue, loss of appetite and nausea. Blood tests revealed ALT 184 U/L, AST 873 U/L, ALP 1041 U/L, GGT 871 U/L and bilirubin 1.7 mg/dL. Viral hepatitis was excluded, and abdominal ultrasonogram was normal. Although hydroxychloroquine was considered unlikely to cause the hepatitis, it was discontinued along with nimesulide, and prednisone was increased to 40 mg per day for 2 weeks. The patient recovered and liver enzymes returned to normal within 8 weeks. Prednisone was gradually tapered off and hydroxychloroquine was subsequently restarted without any rise in liver enzymes.

Case 6

A 57-year-old woman with a past medical history of low back pain due to diffuse lumbar discopathy had been treated for many years with NSAIDs, mainly diclofenac and naproxen. Follow-up tests of liver enzymes had always been normal. When her pain failed to respond to diclofenac and an epidural injection of methylprednisolone and lidocaine, the diclofenac was discontinued, and codeine phosphate 10 mg tid and nimesulide 100 mg bid were prescribed. The patient stopped taking the codeine 2 weeks later, but continued taking the nimesulide with a significant improvement.

Ten weeks later, while still on nimesulide, she developed right abdominal discomfort, anorexia and intermittent vomiting. Nonetheless, she continued her medication for another 2 weeks, when she became jaundiced. On examination she was fully oriented and deeply jaundiced. Laboratory tests revealed serum bilirubin 11.1 mg/dl, of which 7.7 mg/dl was direct, ALT 895 U/L, AST 1,367 U/L, ALP 160 U/L (normal 39–117), GGT 261 U/L (normal 7–49) and lactic dehydrogenase 923 U/L (normal 240–480). Albumin was 40 g/L, globulin 27 g/L and international normalized ratio 2.6. Complete blood count and renal function tests were normal.

The patient was hospitalized, nimesulide was discontinued, and after one week the vomiting ceased. Laboratory tests showed bilirubin 29.5 mg/dl (1.3 direct), ALT 818 U/L, AST 1,420 U/L, ALP 175 U/L, LDH 806 U/L, INR 2.2, albumin 34 g/L, ammonia 80 μg/dl (normal 80–110) and α-fetoprotein 79 ng/ml (normal 0–10). Computerized tomography of the abdomen showed no abnormalities. In the third week she developed ascites, followed by spontaneous bacterial peritonitis with *Klebsiella* pneumonia. Acute hepatic failure with hepatorenal syndrome ensued, and the patient expired in the sixth week of hospitalization.

Discussion

In this report we describe six patients in whom nimesulide was the most likely cause of elevated liver enzymes. Four of them (cases 2–5) had symptomatic hepatitis, and one had a fatal outcome. In three (cases 2, 3 and 6), nimesulide was the only known drug exposure. In another three patients (cases 1, 4 and 5), other drugs were taken concomitantly. However, most of these medications had been prescribed several years prior to the addition of nimesulide and were restarted after the hepatitis had resolved without any rise in liver enzymes. Upon discontinuation of nimesulide, liver enzymes returned to normal in all surviving patients. None of the patients was rechallenged with nimesulide. Patient 6 developed acute hepatic

Table 1. Characteristics of nimesulide-induced liver injury in 6 patients

Case No.	1	2	3	4	5	6	Average ± SD
Age (yr)	61	62	41	70	18	57	51.5 ± 19
Gender	M	F	F	F	F	F	
Nimesulide intake (wk)	9	4	13	2	11	12	8.5 ± 4.5
Peak ALT (U/L)	375	708	643	169	184	895	454 ± 244
Peak AST (U/L)	273	546	359	165	873	1,420	606 ± 470
Peak ALP (U/L)	N	N	N	1,243	1,041	175	460 ± 533
Weeks to ALT normalization	16	9	12	8	8	—	10.6 ± 3.4
Symptoms							
Fatigue		+		+	+	+	
Nausea		+	+	+	+	+	
Vomiting				+		+	
Abdominal pain						+	

N = Normal.

failure, encephalopathy and hepatorenal syndrome and expired 6 weeks after hospitalization. Apparently nimesulide was discontinued too late to prevent the fatal outcome. She received nimesulide for 2 weeks after symptoms of abdominal pain, nausea and vomiting had already developed.

A summary of our data is shown on Table 1. Most patients were middle-aged women (median age 59 years) who developed symptoms of fatigue, nausea and vomiting several weeks (range 2–11) following the initiation of nimesulide therapy. Liver enzymes revealed hepatocellular injury, with a median peak serum ALT of 15 times (range 4–35) the upper limit of normal. Elevated levels returned to normal 2–3 months after discontinuation of the drug.

Data available from studies on nimesulide have shown a mild increase in aminotransferase levels in about 5% of patients [1,5]. These changes were transient and of no clinical significance. Recently however, six cases with nimesulide-induced symptomatic liver injury were reported [6]. Jaundice was the presenting symptom in five of them, two had eosinophilia, and liver biopsies showed hepatocelluar necrosis in four and pure cholestasis in two. All recovered completely after discontinuation of the drug.

The mechanism by which nimesulide induces liver injury is most probably a host idiosyncratic metabolic aberration [7]. This conclusion is based on the rarity of the liver injury, the lack of extrahepatic allergic manifestations or eosinophilia in our patients, and the fact that the injury developed after at least 6 weeks of therapy in four of the six patients. The liver injury was hepatocellular in four cases, cholestatic in one case and mixed in another, in accordance with a previous report [6]. Nonsteroidal anti-inflammatory drugs are known to cause clinically significant liver injury but at a low incidence [8]. However, the enormous consumption of NSAIDs has caused them to be an important class of hepatotoxic drugs. The risk of liver damage depends on the individual drug. For nimesulide, this risk cannot be estimated at this time since no epidemiological information on its consumption in our population is yet available.

In conclusion, our data indicate that nimesulide should be regarded as a likely cause of liver damage. The clinical presentation may vary from an increase in the level of liver enzymes with no symptoms to fatal hepatic failure. The latter grave outcome is probably more likely to follow a continued intake of nimesulide in the presence of symptoms and abnormal liver function tests. In view of the above, monitoring of liver enzymes after initiating therapy with nimesulide seems essential.

References

1. Davis R, Brogden RN. Nimesulide: an update of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1994;48(3):431–54.
2. Magni E. The effect of nimesulide on prostanoid formation. *Drugs* 1993;46(Suppl 1):10–14.
3. Pochobradsky MG, Mele G, Beretta A. Post-marketing survey of nimesulide in the short term treatment of osteoarthritis. *Drugs Exper Clin Res* 1991;17(3):197–204.
4. Fusetti G, Magni E, Armandola MC. Tolerability of nimesulide. Epidemiological data. *Drugs* 1993;46(Suppl 1):277–80.
5. Lucker PW. Double-blind, randomized, multicenter clinical study evaluating the efficacy and tolerability of nimesulide in comparison with etodolate in patients suffering from osteoarthritis of the knee. *Eur J Rheumatol Inflamm* 1994;14(2):29–38.
6. Van Steenbergen W, Peeters P, De Bondt J, Staessen D, Buscher H, Laporta T, Roskmas T, Desmer V. Nimesulide induced acute hepatitis: evidence from 6 cases. *J Hepatol* 1998; 29(1):135–41.
7. Zimmerman HJ, Maddrey WC. Toxic and drug induced hepatitis. In: Schiff L, Schiff ER, eds. Diseases of the Liver. 7th ed. Philadelphia: JB Lippincott Company, 1993:707–83.
8. Manoukian AV, Carson JL. Nonsteroidal anti-inflammatory drug-induced hepatic disorders: incidence and prevention. *Drugs Safety* 1996; 15(1):64–71.

Correspondence: Dr. S. Bar-Meir, Head, Dept. of Gastroenterology, Sheba Medical Center, Tel-Hashomer 52621, Israel. Tel: (972-3) 530 2679; Fax: (972-3) 530 3070; email: gastro@netvision.net

So then Dr Froyd said that all I needed was to cultivate a few inhibitions and get some sleep.

Anita Loos (1888–1981), U.S. novelist and scriptwriter.
Gentlemen Prefer Blondes (1925).