Acute Liver Failure Associated With Prolonged Use of Bromfenac Leading to Liver Transplantation

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Bromfenac, a nonnarcotic analgesic nonsteroidal anti-inflammatory drug, was associated with reversible, minor elevations in serum aminotransferase levels during clinical trials. The aim of this study is to describe the clinical, laboratory, and histological features of 4 patients with severe bromfenac hepatotoxicity identified at 3 tertiary care centers participating in the US Acute Liver Failure Study Group. Bromfenac was administered for chronic musculoskeletal disorders to 4 women in therapeutic doses of 25 to 100 mg/d for a minimum of 90 days. All patients reported a prodrome of malaise and fatigue and presented with severe, symptomatic hepatocellular injury with associated hypoprothrombinemia. None of the subjects had underlying liver or kidney disease, and there was no evidence of a hypersensitivity reaction. Other identifiable causes of acute liver failure were uniformly excluded. Despite supportive measures, all the subjects developed progressive liver failure over 5 to 37 days, leading to emergency liver transplantation in 3 patients and death in 1 patient while awaiting transplantation. Extensive confluent parenchymal necrosis that appeared to begin in the central zones and was accompanied by a predominantly lymphocytic infiltrate was noted in all the livers examined. Nodular regeneration was seen in the 2 patients with a more protracted clinical course. Administration of therapeutic doses of bromfenac for greater than 90 days was associated with the development of acute liver failure leading to liver transplantation or death in 4 adult women. The poor outcomes observed in this series, coupled with the inability to identify individuals at risk for severe, idiosyncratic bromfenac hepatotoxicity, preclude further use of bromfenac in the medical community.
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Bromfenac (Duract; Wyeth-Ayerst Laboratories, Philadelphia, PA), a potent peripherally acting nonnarcotic analgesic nonsteroidal anti-inflammatory drug (NSAID), was approved for use in the United States in July 1997.[1,2] More than 2.5 million prescriptions for bromfenac were written until June 1998, when the drug was voluntarily withdrawn by the manufacturer because of postmarketing reports of severe hepatotoxicity.[3] Only one case of severe hepatotoxicity caused by bromfenac use has been reported in the medical literature.[4] We now describe the clinical presentation, laboratory findings, and liver histological characteristics of 4 patients receiving daily therapeutic doses of bromfenac who developed acute liver failure leading to liver transplantation or death.[5]

The Acute Liver Failure Study Group (ALFSG) is a cooperative effort of 14 major US academic medical centers assembled to gather data regarding the cause, treatment, and outcome of patients with acute liver failure.[6] In January 1998, the ALFSG began collecting prospective demographic and clinical data from patients with acute liver failure presenting to participating centers. From January 1998 through July 1998, a total of 53 cases of acute liver failure were identified by the ALFSG. Eleven cases (21%) were attributed to idiosyncratic drug reactions. Four cases of acute liver failure attributed to bromfenac ingestion were identified and form the basis of this report.

Case Reports

Case 1

A 40-year-old Hispanic woman took bromfenac, 75 mg daily, for chronic shoulder pain for 3 months. Two weeks before hospitalization, she was prescribed amoxicillin for a presumed upper respiratory infection. She took a total of 4 doses of amoxicillin and 3 doses of acetaminophen (1500 mg total). She denied a history of occupational exposure to hepatotoxins, intravenous drug use, recent alcohol consumption, or foreign travel. Two years before presentation, she was noted to have normal serum aminotransferase levels. At the time of hospitalization, she was afebrile, jaundiced, and lethargic. Bromfenac and all other medications were immediately discontinued. Laboratory examination showed the following values: alanine aminotransferase (ALT), 2983 U/L; aspartate aminotransferase (AST), 1823 U/L; alkaline phosphatase (AP), 133 U/L; albumin, 2.8 g/dL; prothrombin time (PT), 65 seconds (international normalized ratio [INR], 8.9); and total bilirubin, 18 mg/dL. Her white blood cell count was normal, without eosinophilia. Serum acetaminophen level was undetectable. Serological evaluation for hepatitis (A, B, and C), cytomegalovirus (CMV), herpes simplex virus, Epstein-Barr virus (EBV), Wilson's disease, and autoimmune hepatitis was unremarkable. An abdominal ultrasound showed no hepatic or biliary abnormalities.

Within 72 hours of transfer to the University of Michigan Medical Center (Ann Arbor, MI), her mental status and liver function deteriorated, and she underwent liver transplantation. The explant showed extensive multilobular confluent necrosis, but in the areas with viable hepatocytes, the necrosis primarily involved the centrilobular areas. Marked microvesicular steatosis of the nonnecrotic hepatocytes and a diffuse lobular hepatitis with sinusoidal lymphocytosis was observed (Fig. 1). The patient is doing well 6 months posttransplantation.

Case 2

A 40-year-old Caucasian woman was prescribed bromfenac, 25 mg twice daily, for chronic bilateral shoulder and musculoskeletal pain. Over the next 8 months, she experienced excellent pain relief. Her only other medication was a sedative containing acetaminophen (325 mg) and diphenhydramine for sleep disturbance. At an outpatient visit 8 weeks before presentation, her serum AST level was 112 U/L. Two weeks before presentation, she developed fatigue, jaundice, and weakness and stopped taking bromfenac. However, she experienced worsening malaise with nausea, leading to hospitalization. She denied a history of chronic alcohol use, intravenous drug use, recent travel, or exposure to known hepatotoxins. On examination, she was afebrile, well nourished, and jaundiced. Laboratory evaluation showed the following values; AST, 2112 U/L, ALT, 4570 U/L; total bilirubin, 7.0 mg/dL; PT, 21 seconds (INR, 2.7), and AP, 120 U/L. Serological evaluation for hepatitis (A, B, and C), Wilson's disease, CMV, EBV, and autoimmune hepatitis were negative. An abdominal ultrasound was unremarkable.

Within 3 days of hospitalization at the University of Michigan Medical Center, her clinical condition deteriorated, and she required mechanical ventilation for cerebral edema. At liver transplantation 6 days after presentation, her liver was noted to be small and atrophic. Liver histological examination showed nearly total necrosis of the liver parenchyma, with intense periportal and parenchymal lymphocytosis. Three months after transplantation, she is slowly recovering.

Case 3

A 46-year-old Caucasian woman developed fatigue, nausea, and jaundice over 2 weeks. She denied a history of
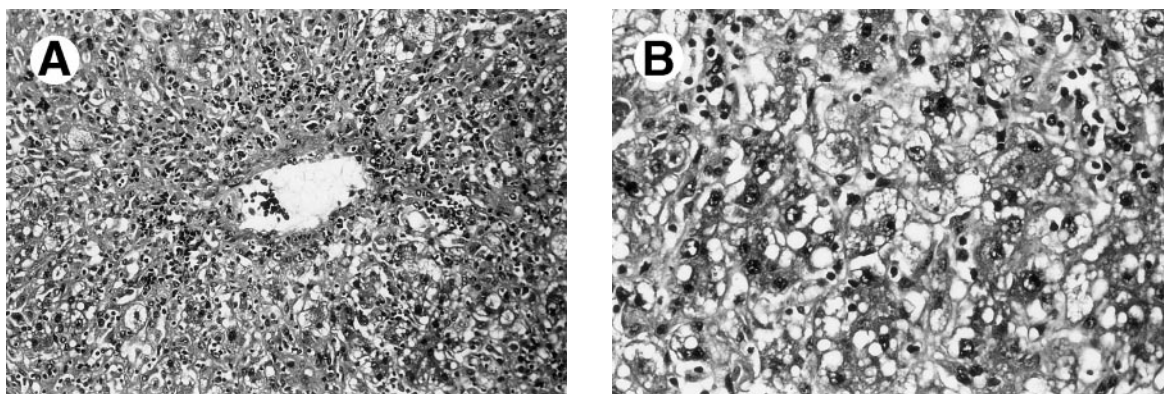

Figure 1. Histological findings from the liver explant of patient 1. (A) Severe centrilobular necrosis with parenchymal collapse. (Hematoxylin and eosin, original magnification ×20) (B) Prominent microvesicular steatosis of nonnecrotic hepatocytes with accompanying lobular hepatitis and sinusoidal lymphocytosis. (Hematoxylin and eosin, original magnification ×40)

liver disease, exposure to occupational hepatotoxins, intravenous drug use, or recent travel. She had a remote history of regular alcohol ingestion, but had been abstinent for 15 years. In the 3 months before presentation, she had taken 25 to 50 mg of bromfenac daily and one to two codeine with acetaminophen (325 mg) tablets daily for chronic shoulder pain. At presentation, she was a chronically ill-appearing woman with proximal muscle wasting and jaundice. Laboratory values included the following: AST, 1101 U/L; ALT, 911 U/L; AP, 186 U/L; and total bilirubin, 6.9 mg/dL. PT was elevated at 18.5 seconds; INR, 2.4; and serum albumin level was 2.8 g/dL. Serum acetaminophen level was undetectable. Serological evaluation for hepatitis (A, B, C, and E), CMV, EBV, Wilson's disease, and autoimmune hepatitis was unremarkable. An abdominal ultrasound showed a thickened gallbladder wall.

Four weeks after presentation, the patient was transferred to the University of Nebraska Medical Center (Omaha, NE) for further evaluation and treatment. Laboratory values included AST, 331 U/L; ALT, 305 U/L; and total bilirubin, 28.3 mg/dL. A transjugular liver biopsy specimen showed prominent pericentral collapse with lobular and periportal lymphocytosis. Despite supportive care, the patient developed progressive encephalopathy and coagulopathy over the next 3 weeks, requiring liver transplantation. Evaluation of her explant showed minimal periportal inflammation, but prominent lymphocytosis in the areas of collapse. Nodular regeneration with early septate scars accompanied the confluent necrosis. Six months after transplantation, she continues to improve.

Case 4

A 60-year-old Caucasian woman was hospitalized with abdominal pain, jaundice, and syncope.[7] She had been prescribed bromfenac, 25 mg four times daily, for arthritic pain for 3 months before presentation. Her past medical history included long-standing rheumatoid arthritis, anxiety, and prior thyroidectomy, for which she was receiving alprazolam, estrogen, progesterone, and levothyroxine. There was no history of liver disease,

alcohol use, intravenous drug use, recent travel, or occupational exposure to hepatotoxins. At presentation, she was jaundiced, without evidence of hepatosplenomegaly or skin rash. Laboratory values included AST, 601 U/L, and total bilirubin, 2.9 mg/dL. There was no peripheral eosinophilia, and serum acetaminophen level was undetectable. Serological evaluation for hepatitis (A, B, C, and E), CMV, and herpes simplex virus was negative, and ultrasound examination was unremarkable. The antinuclear antibody count was mildly positive at 1:160, and smooth-muscle antibody was undetectable. Bromfenac was discontinued and despite initial treatment with prednisone, 20 mg/d, the serum AST level increased to 1810 U/L, and bilirubin level increased to 10 mg/dL.

On hospital day 17, a transjugular liver biopsy at Oregon Health Sciences University (Portland, OR) showed bridging necrosis with nodular regeneration and periportal lymphocytosis, but minimal lobular inflammation. Prednisone therapy was discontinued, but unfortunately the patient developed progressive ascites and encephalopathy and died of multiorgan failure on hospital day 37. At postmortem, the liver weighed 700 g and histological evaluation showed submassive hepatic necrosis with residual islets of hepatocytes and a lymphocytic infiltrate in areas of collapse, but not in the regenerative nodules.

Discussion

The daily dose of bromfenac administered to these patients with severe hepatotoxicity was within the recommended prescribing guideline of less than 150 mg/d.[2] However, each subject took bromfenac for periods of time exceeding the 10-day maximum recommended by the manufacturer, and serial monitoring of aminotransferase levels was not routinely performed (Table 1). None of the subjects had known liver or kidney disease, and none were receiving other medications, such as cimetidine or phenytoin, that are known to alter the bioavailabil-

Table 1. Clinical Features and Outcome With Severe Bromfenac Hepatotoxicity

Patient No.	Age (yr)/Sex	Race	Duration of Use (mo)	Daily Dose (mg)	Max ALT (U/L)	Max PT (INR)	Max Bili (mg/dL)	Days to Outcome*	Outcome
1	40/F	H	3	75	2983	8.9	18	5	Transplant
2	42/F	C	10	50	4570	4.1	47	6	Transplant
3	46/F	C	3	50	911	4.0	50	33	Transplant
4	60/F	C	3	100	1380	4.1	25	37	Death

Abbreviations: H, Hispanic; C, Caucasian; Max, maximum; Bili, bilirubin.
*Days from hospitalization to identified outcome.

ity of bromfenac.[2,8] A thorough evaluation in each case failed to show another identifiable cause of acute liver failure. Although subjects 1, 2, and 3 received therapeutic doses of acetaminophen for short periods of time, the progressive nature, clinical course, and histological findings observed are not consistent with surreptitious acetaminophen hepatotoxicity.[9] All the subjects denied a history of intolerance to other NSAIDs, and none had evidence of a hypersensitivity reaction. Although none of the subjects were rechallenged with bromfenac, the temporal relationship between bromfenac use and the development of liver injury are suggestive of an idiosyncratic reaction to bromfenac as the presumed cause of liver failure.[10,11]

The observation that all of the afflicted patients were adult women may relate to the demographics of NSAID use.[12,13] The severe hepatocellular injury pattern at presentation and the progressive coagulopathy and encephalopathy observed in all patients is consistent with a clinical syndrome of acute liver failure.[14] Despite prompt discontinuation of bromfenac and supportive care, none of the subjects spontaneously recovered.

Liver histological examination correlated with the duration of clinical illness (Table 2). The 2 subjects with the most rapid clinical deterioration (subjects 1 and 2) had the most severe necrosis and collapse, whereas the 2 subjects with a more protracted clinical course (subjects 3 and 4) showed evidence of nodular hepatic regeneration. All the livers showed extensive confluent parenchymal necrosis that possibly began in the central zone, suggestive of a toxic cause. In addition, an intense lobular and periportal hepatitis composed predominantly of lymphocytes was noted. A similar heterogeneity of histological findings in patients presenting with acute liver failure caused by drugs and other causes has been noted.[15]

Severe NSAID hepatotoxicity leading to hospitalization or death is rare. However, because of their enormous worldwide consumption, NSAIDs have become an important class of drugs responsible for drug-induced liver injury.[12] During clinical trials, bromfenac, like other NSAIDs, was associated with a mild elevation in serum aminotransferase levels (<3 times the upper limit of normal [ULN]) in up to 15% of treated patients.[2] Moderate to severe serum aminotransferase elevations (>3 times ULN) were noted in 2.7% of treated patients and marked elevations (>8 times ULN) in 0.4% of treated patients. The serum aminotransferase elevations appeared to be reversible on cessation of bromfenac use. The incidence of severe bromfenac hepatotoxicity is unknown because sporadic cases may be underreported, and aminotransferase monitoring is not commonly performed in patients receiving NSAIDs.

The association of prolonged use of bromfenac with the development of severe hepatotoxicity in our series and other reports suggests that a toxic metabolite may be involved in the etiopathogenesis.[4,16] Bromfenac, a benzene acetic acid derivative, is rapidly and extensively metabolized in the liver after absorption from the intestinal lumen. Although the hepatic enzyme(s) responsible for bromfenac metabolism in vivo are not well characterized, glucoronide conjugates of aglycone metabolites of bromfenac can be detected in the urine after oral ingestion.[17] The striking microvesicular steatosis in the liver tissue of one of the study subjects (subject 1) is similar to that described in other cases of idiosyncratic NSAID hepatotoxicity.[18,19] However, whether the steatosis reflects drug-induced mitochondrial toxicity or is simply a marker of NSAID use is unclear.[20,21]

Other NSAIDs have been withdrawn from the marketplace because of an unacceptably high rate of severe or fatal hepatotoxicity reported during postmarketing surveillance.[22] The failure to detect such severe hepatotoxicity during drug development in part relates to the relatively short time during which patients are studied, the small num-

Patient No.	Multilobular Necrosis/Collapse	Lobular Inflammation	Periportal Inflammation	Steatosis	Nodular Regeneration	Liver Weight (g)
1	++++	+++	+	+++	−	500
2	++++	+++	++	+	−	440
3	++++	+	−	+	++	820
4	++++	+	+	−	++	700

Table 2. Histological Features of Severe Bromfenac Hepatotoxicity

bers of patients involved in clinical trials, and the infrequent occurrence of such severe reactions.[23] The patients reported in this case series had severe hepatotoxicity at presentation that did not improve despite drug cessation and supportive measures. Female sex and daily bromfenac use in excess of 90 days were the only identifiable risk factors. The poor outcomes observed in this series, coupled with the inability to identify individuals at risk, precludes the continued use of bromfenac in the general medical community.

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Appendix

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