

Idiosyncratic toxic hepatitis secondary to single dose of naproxen

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Naproxen is a member of the propionic acid derivative NSAIDs. Among other members of this group are ibuprofen, ketoprofen, flurbiprofen and benoxaprofen. They are generally well tolerated except for benoxaprofen, which has been withdrawn from the market secondary to fatal hepatic toxicity (1).

A 57 year-old-woman presented with dull abdominal pain and jaundice. On Day 1 of the abdominal pain she took one tablet of naproxen. Although abdominal pain gradually improved, on Day 6 she started to have generalized itching associated with jaundice and darkening of the urine. She was admitted to the hospital on Day 10. On admission, she had icteric skin and sclera. Laboratory revealed alanine-aminotransferase 2196 IU/L (normal 10-70), aspartate-aminotransferase 442 IU/L (normal 12-50), gamma-glutamyl transpeptidase 442 IU/L (normal 7-60), lactate dehydrogenase 960 IU/L (normal 101-450), alkaline phosphatase 80 IU/L (normal 25-100), bilirubin (total/direct) 22/14 mg/dl, total protein 6,5 gr/dl, and albumin 4,2 g/dl. Urine had 3+ bilirubin and urobilinogen. Anti-hepatitis A IgG was positive, hepatitis B surface antigen, hepatitis B surface antibody, anti-HBc- IgM, anti-hepatitis C antibody, hepatitis C-RNA, anti HIV antibody, antinuclear antibody, cytomegalovirus and Epstein Barr virus IgM and IgG antibodies were all negative. Ultrasound and computerized tomography of the abdomen were unremarkable. She underwent liver biopsy, which disclosed histopathological findings of toxic hepatitis (Fig. 1). There was mild macrovesicular steatosis, rare single cell necrosis, hepatocellular and canalicular yellow-brown pigmentary accumulation, as well as significant enlargement of the portal areas with mononuclear cell infiltration along with eosinophils and piecemeal necrosis. Bilirubin staining showed mild hepatocellular and canalicular cholestasis. Total bilirubin and liver enzymes normalized by week 20 (Table 1).

The mechanism of naproxen induced hepatotoxicity in humans is not completely understood. In general, idiosyncratic hepatotoxic drug reactions involve 2 major mechanisms (2) : unusual metabolism of the drug and immune mediated hepatotoxicity (allergic hepatitis). In the first type, toxicity may appear with the first administration of the drug. In the second type, the adverse effects usually become evident after previous asymptomatic contacts and it needs a period of sensitization (2). In addition, skin rash and fever usually accompanies the

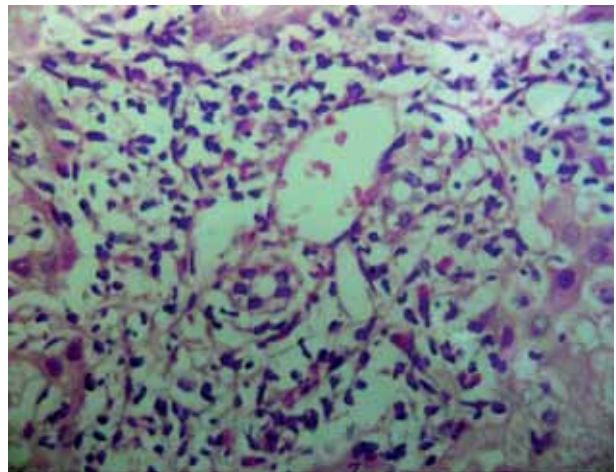


Fig. 1.

immune mediated liver toxicity (3). In our patient, there was no hypereosinophilia in the peripheral blood. In the liver biopsy, although there were some eosinophils in the portal areas, there were no eosinophilic infiltrates. Moreover, there were no clinical manifestations of hypersensitivity, such as fever and rash. Hence, findings were mostly consistent with metabolic type of idiosyncratic hepatic toxicity. Only few hepatotoxic side effect of the naproxen have been previously reported (4-7). In these reports, hepatotoxicity was mainly characterized by cholestasis and hepatocellular necrosis. In our patient, hepatotoxicity was characterized by hepatocellular injury.

In conclusion, naproxen is generally safe but may be a potentially hepatotoxic drug and this effect is probably idiosyncratic. This case is unique because hepatotoxicity occurred after only a single dose of naproxen.

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Table 1. — Course of the liver function tests

TEST	WEEK					
	0	1	2	10	14	20
AST ^a	2196	1744	636	218	76	22
ALT ^b	2023	1549	622	183	97	17
GGT ^c	442	235	195	554	290	47
ALK P ^d	80	58	65	72	47	17
T.BIL ^e	22	32	37	1,4	0,6	0,7

(a) Aspartate-aminotransferase, (normal 12-50); (b) Alanine-aminotransferase, (normal 10-70); (c) Gammaglutamyl transpeptidase, (normal 7-60); (d) Alkaline phosphatase, (normal 25-100); (e) Total bilirubin.

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