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Clinical Studies

Ornidazole-induced liver damage: report of three cases and review of the literature

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Abstract: Metronidazole and ornidazole, synthetic nitroimidazole derivatives, are used in the treatment of infections caused by anaerobic bacteria and protozoa. The drugs are well tolerated and serious side effects are very rarely encountered. Hepatotoxicity is a rare side effect and hitherto only six cases have been reported. We describe three patients who developed hepatitis after ornidazole use and review the previously reported cases. All three cases used ornidazole in conventional doses and developed hepatitis and associated cholestasis. They improved 1–2 months after discontinuation. We concluded that nitroimidazole derivatives may cause hepatotoxic damage resembling acute cholestatic hepatitis. Early recognition and withdrawal of the drug may prevent further damage.

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Metronidazole and ornidazole, synthetic nitroimidazole derivatives, are used in the treatment of infections caused by anaerobic bacteria and protozoa. The drugs are generally well tolerated. The most frequent side effects are an unpleasant taste, nausea, vomiting, abdominal discomfort, and diarrhea. Serious side effects such as seizures and peripheral neuropathy are very rarely encountered in conventional doses (1).

Hepatotoxicity is a rare side effect. Up to now, only six cases have been reported in the English-language literature (Medline 1966–2002): metronidazole was the drug in four (2–5), ornidazole in one (6), and both drugs in the other (7). Here, we describe three patients who developed hepatitis after ornidazole use and review the previously reported cases.

Case reports

Case 1

A 38-year-old woman was diagnosed as having vaginitis and given fluconazole (single dose) and ornidazole. Nine days later, she was admitted with fever, diarrhea, abdominal pain, and malaise. Microscopic examination of the stool revealed *Entamoeba histolytica* cysts and ornidazole 1 g/day was administered for 4 days, but she felt worse and was re-admitted on the third day of treatment. She had a history of acute hepatitis A 14 years ago and was immune against hepatitis B with vaccination. Physical examination revealed scleral jaundice and hepatomegaly (the edge of the liver was palpable 3 cm below the right costal margin in inspiration). Laboratory examination revealed the following: ALT 977 U/l, AST 1288 U/l, total bilirubin 32 mg/dl with a conjugated fraction of 19 mg/dl, alkaline phosphatase 1062 U/l (normal: 38–145), γ-GT 551 U/l (7–32), Hb 9.2 g/l, WBC 7400/mm^3 (64% PNL, 34% lymphocytes, 2% monocytes), platelets 252 000/mm^3, prothrombin time 22 s (33%). Serology revealed anti-HAV IgM (−)/IgG (+), anti-HBs (+), anti-HCV, HCV-RNA, FANA, anti-smooth muscle antibody (ASMA), and IgM antibodies against HSV, CMV, and EBV VCA negative. The intra- and extrahepatic biliary system was normal in MR cholangiography. Percutaneous liver biopsy revealed cholestasis with severe hepatocyte swelling and rosette formation, pericellular and periportal bridging fibrosis, and a moderate degree of portal inflammation composed of mononuclear cells, neutrophil polymorphs around the proliferated ductules, and sparse eosinophils (Fig. 1). Orni-

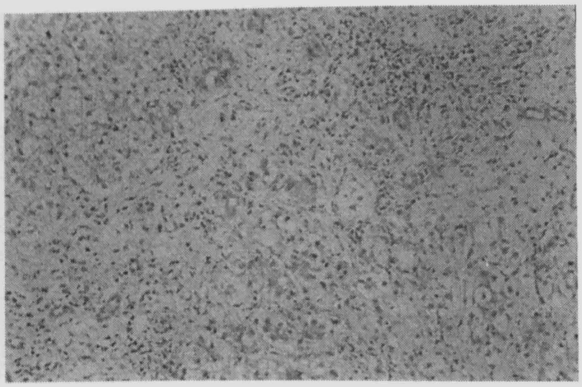

Fig. 1. (Case 1) Feathery degeneration and cholestatic rosette formation in acinar cells (left top and right bottom), inflamed, enlarged, bridged portal tracts with ductular proliferation (right top and left bottom) (HE × 200).

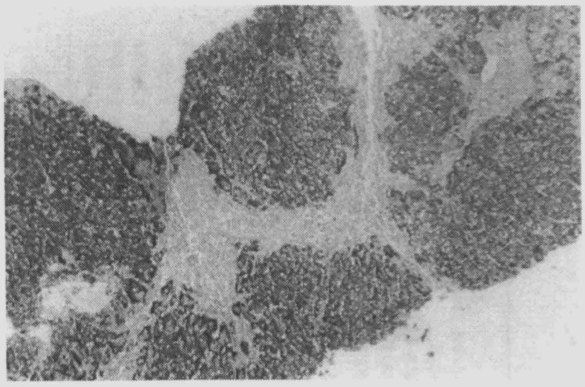

Fig. 2. (Case 2) Confluent and bridging parenchymal necroses (paler areas) (PAS × 100).

dazole treatment was discontinued, and within 1 month transaminase and bilirubin levels returned to normal. During a follow-up of one and a half years, she has been doing well without any significant abnormality in physical examination.

Case 2

A 50-year-old woman presented with development of jaundice, dark urine, and fatigue gradually in the preceding 7 days. Three weeks ago, she reportedly was prescribed ornidazole (1 g/day for 3 days) for her vaginitis. She completed the course and discontinued the drug. She reported a history of acute hepatitis following ornidazole use of 7 days 10 years ago. Physical examination revealed jaundice and liver enlargement (2 cm). Laboratory studies were as follows: ALT 3042 U/l, AST 1665 U/l, total bilirubin 47.9 mg/dl, direct bilirubin 19.3 mg/dl, alkaline phosphatase 422 U/l, γ-GT 156 U/l, WBC 9200/mm^3 (63% PNL, 37% lymphocytes), Hb 14 g/dl, platelets 252 000/mm^3, prothrombin time 16.5 s (50%). HBsAg, anti-HBc IgM and IgG, anti-HAV IgM and IgG, anti-HCV, HCV-RNA, anti-HEV, FANA, ASMA, anti-LKM, and IgM antibodies against CMV and EBV VCA all remained negative. An upper abdominal USG did not show any abnormality. Percutaneous liver biopsy revealed severe hepatocyte swelling with sparse canalicular bile plugs and rosetting, confluent and bridging type hepatocyte necrosis connecting terminal hepatic venules to the neighboring ones or to portal tracts, portal inflammation composed mainly of mononuclear cells and also of neutrophil and eosinophil polymorphonuclear leukocytes, and proliferation and mild inflammation of bile ductules (Fig. 2). Fifty-two days after discontinuation of ornidazole treatment, transaminase and bilirubin levels returned to normal. During a follow-up of 8 months, all the liver abnormalities returned to normal and she was in good health.

Case 3

A 25-year-old woman was diagnosed as having vaginitis and prescribed ornidazole (1 g/day) for 3 days. Fifteen days later, she presented with jaundice, dark urine, and vomiting. She denied any previous exposure to toxic materials, any other drug, and was a teetotaler. Physical examination revealed scleral jaundice. Laboratory studies showed ALT 1160 U/l, AST 790 U/l, total bilirubin 10.1 mg/dl, conjugated bilirubin 8.7 mg/dl, alkaline phosphatase 431 U/l, γ-GT 99 U/l, Hct 34%, WBC 6700/mm^3 (66% PNL, 30% lymphocytes, 4% monocytes), platelets 270 000/mm^3, prothrombin time 15 s (100%), and anti-HAV IgM (−)/IgG (+). HBsAg, anti-HBc IgM and IgG, anti-HCV, HCV RNA, anti-HEV, ANA, ASMA, anti-LKM, and IgM antibodies against CMV, and EBV VCA all remained negative. The intra- and extrahepatic biliary system was normal in MR cholangiography. Percutaneous liver biopsy revealed mild cholestasis with hepatocyte swelling, multiple focal and sparse confluent necroses mostly around the terminal hepatic venules, increase in sinusoidal lining cells, and moderate portal inflammation composed of mononuclear cells and neutrophil and eosinophil polymorphonuclear leukocytes (Fig. 3). One month later, transaminase and bilirubin levels returned to normal. During a follow-up of 1 year, she has been doing well without any liver abnormality.

Discussion

Although drugs are usually metabolized in the liver without any injury, drug-related injuries are

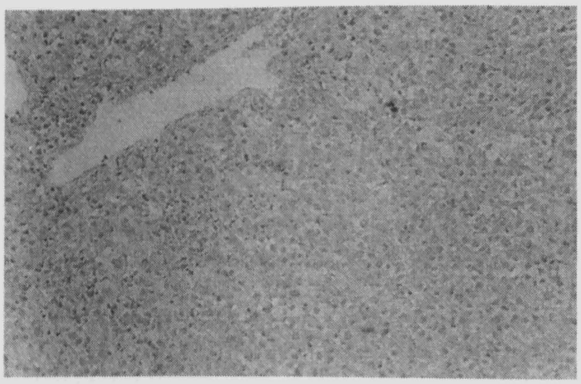

Fig. 3. (Case 3) Parenchymal degeneration and focal necroses around a terminal hepatic venule (HE × 200).

rare. These are usually mild and subclinical. Serious consequences and even death may occur rarely. Drug reactions are divided into two basic types – type A reactions, which are predictable, common, and related to the pharmacologic action of the drug; and type B reactions, which are unpredictable, non-dose-dependent, uncommon, and generally not related to any pharmacologic action, with several subclassifications. Most hepatotoxins act through type B reactions (8, 9).

In the adult population, drug-induced liver disease is responsible for 10–50% of sporadic liver enzyme elevations (10). Nitroimidazole derivatives are used in a wide range of disorders, and hepatic adverse effects are not frequent. Only six patients have been reported previously (2–6): metronidazole was taken as an overdose (12.5 g) in one (4), and ornidazole induced autoimmune hepatitis in another (6). The characteristics of the patients previously reported and also those of our patients are summarized in Table 1. A careful investigation failed to reveal any risk factor or underlying liver diseases such as viral hepatitides, alcohol use, obesity, diabetes, herbal drug use, and other medications in all our cases studied.

Drug-induced liver injury has three characteristics: (1) absence of baseline liver abnormality, (2) temporal relationship to the use of the drug, and (3) improvement upon withdrawal. Recurrence with incidental re-challenge confirms the diagnosis; however, it is unethical to be intentional (11). Case 2 in this report had a history of a previous reaction following ornidazole use, like the patient described by Ersoz et al. (7), who used metronidazole and ornidazole at separate times and both resulted in hepatotoxic reactions.

Although nitroimidazole derivatives are metabolized in the liver and their half-lifes are not altered in patients with renal failure, the hydroxy

Table 1. Summary of cases with nitroimidazole-induced hepatic injury

Case no (reference no)	Age/sex	Drug	Dose	Duration	Total bilirubin (mg/dl)	ALT (U/l)	AST (U/l)	Liver biopsy	Outcome
1 (2)	58/M	Metronidazole	2 g/day	4 days	0.9	720	735	—	Improved in 3 weeks
2 (3)	68/F	Metronidazole	500 mg/day	4 days	Normal	650	1450	—	Improved in 2 weeks
3 (4)	58/F	Metronidazole	12.5 g	Single dose	2.1	2570	6120	—	Improved in 4 weeks
4 (5)	24/F	Metronidazole	NA	NA, two times, 2 years apart	7.9	5278	4439	—	Liver failure, exitus
5 (6)	35/F	Ornidazole	(a) NA	(a) 6 days	(a) 17	(a) 1140	(a) 1260	(a) Mild inflammation, no fibrosis	(a) and (b) Improved in 4 weeks
			(b) 500 mg/day	(b) 4 days	(b) 16	(b) 1255	(b) 1671	(b) Minimal inflammation, moderate steatosis	
6 (7)	36/F	(a) Metronidazole	(a) 1.5 g/day	(a) 5 days	(a) 16	(a) 550	(a) 800	(a) Acute hepatitis	(a) Improved in 4 weeks
		(b) Ornidazole	(b) NA	(b) 10 days	(b) 3.64	(b) 1066	(b) 1163	(b) Chronic hepatitis (portal fibrosis, piecemeal necrosis)	(b) Improved in 16 weeks
		(c) Ornidazole	(c) 1.5 g/day	(c) 7 days	(c) 6.1	(c) 1359	(c) 1270	(c) Chronic autoimmune hepatitis	(c) Improved in 20 weeks
7 (PR-1)	38/F	Ornidazole	1 g/day	4 days	32	977	1288	Cholestasis with moderate inflammation, prominent fibrosis, and ductular proliferation	Improved in 4 weeks
8 (PR-2)	50/F	Ornidazole	1 g/day	3 days	47.9	3042	1665	Mild cholestasis with focal and bridging parenchymal necrosis, moderate portal inflammation	Improved in 7 weeks
9 (PR-3)	25/F	Ornidazole	1 g/day	3 days	10.1	1160	790	Mild cholestasis with focal and confluent necroses and moderate inflammation	Improved in 4 weeks

M: male, F: female, NA: not available, PR: present report.

metabolites were said to accumulate and a patient on hemodialysis was reported to develop nitroimidazole-induced toxicity (3). This patient had antibodies against the hepatitis C virus as well.

Liver injury may be cytolytic, cholestatic, or mixed. All our three patients had both cytolytic and cholestatic laboratory findings. The drugs may trigger an autoimmune hepatitis as previously described by Kosar et al. (6). Their patient developed an autoimmune hepatitis after ornidazole use and was managed successfully by corticosteroids. She reportedly developed another attack 3 years later following ornidazole use again.

Our first patient used fluconazole as well. This drug has been reported in association with liver injury, especially in severely immunodepressed patients (12, 13). However, clinical liver injury risk seems to be much less frequent in the normal population: a cohort study based on general practice database revealed no liver injury after use by 35 833 patients (13). She took only a single dose of fluconazole (150 mg). After 9 days, she became symptomatic after ornidazole use. When she was admitted with gastrointestinal tract symptoms, there was no evidence of liver injury and we concluded that fluconazole did not seem to be responsible for the liver injury.

Female gender was reported as an important risk factor for the development of drug-induced hepatitis, with a female:male ratio of 4:1. All our three patients and the previously reported five out of six cases were female. However, the relatively more common indication of metronidazole or ornidazole use (such as vaginitis) in women may create a bias.

In conclusion, ornidazole, a frequently used nitroimidazole derivative, may cause hepatotoxic damage resembling acute cholestatic hepatitis. Early recognition and withdrawal of the drug may prevent further damage.

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