Severe hepatitis with prolonged cholestasis and bile duct injury due the long-term use of ornidazole

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Abstract

Nitroimidazole derivatives are commonly used in the treatment of protozoal and anaerobic infections, and reports of their hepatotoxicity are rare. We report a case of severe hepatitis due to the long-term (8 weeks) use of ornidazole. A 27-year-old woman presented for evaluation of elevated serum transaminase and total bilirubin levels. Liver biopsy revealed portal inflammation, hepatocellular and canalicular cholestasis, porto-portal and porto-central bridging fibrosis, and a tendency to form nodules. No aetiological factors associated with chronic liver disease were identified. The abdominal ultrasonographic findings were compatible with chronic liver disease. We therefore made the diagnosis of severe hepatitis resulting from the long-term use of ornidazole. We conclude that nitroimidazole derivatives may lead to serious liver damage, especially in female patients. (Acta gastroenterol. belg., **2007**, 70, **293-295**).

Key words : ornidazole, hepatitis, nitroimidazole, hepatotoxicity.

Introduction

The severity of drug-induced liver injury varies from minor, non-specific changes in hepatic structure and function to fulminant hepatic failure, cirrhosis, and liver cancer. Women are approximately four times more prone to drug-induced chronic hepatitis than men. The duration of drug ingestion may be a risk factor (1).

Ornidazole is a synthetic nitroimidazole derivative used in the treatment of anaerobic and protozoal infections. Although it has been reported that nitroimidazole derivatives have side effects (such as neurotoxicity, glossitis, and stomatitis) hepatotoxicity related to these drugs has been rarely reported (2-4).

It has been reported that ordinazole-induced hepatotoxicity develops after short-term use (5-7). However, we report a case of severe hepatitis with prolonged cholestasis and bile duct injury likely due to the long-term (8 weeks) use of ornidazole.

Case report

A 27-year-old woman presented to our clinic in November 2005 for evaluation of jaundice, fatigue, and nausea. She had been given ornidazole (250 mg bid) for 8 weeks for intestinal amoebiasis. Routine baseline values obtained 3 months before this treatment confirmed that liver enzyme activities and abdominal ultrasonographic findings were normal. The patient had no history of obesity, alcohol, or any medication use except ornidazole. Jaundice and hepatosplenomegaly were note on physical examination ; vital signs were normal.

The results of laboratory tests were as follows : alanine aminotransferase (ALT), 1593 U/l ; aspartate aminotransferase (AST), 2434 U/l ; alkaline phosphatase, 532 U/l ; γ-glutamyl transpeptidase, 199 U/l ; total bilirubin, 28.6 mg/dl ; direct bilirubin, 14.5 mg/dl ; total protein, 5.8 g/dl ; albumin, 3.5 g/dl ; and prothrombin time, 25.4 seconds. The complete blood count, blood glucose, urea, and creatinine levels were within normal limits. Serologic tests, including anti-hepatitis A virus (HAV) IgM, hepatitis B surface antigen (HBsAg), anti-hepatitis B core antigen, anti-hepatitis B surface antigen, hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR), anti-hepatitis C virus (HCV), HCV-RNA, anti-human immunodeficiency virus (HIV), *Brucella* tube agglutination, Widal's test for *Salmonella*, IgM antibodies against herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) VCA, were all negative. Auto-antibodies (antinuclear antibodies (ANA), anti-double strand (anti-ds) DNA, anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), and anti-liver-kidney microsomal (LKM1) antibody) were negative. Immunoglobulins (IgA, IgG, and IgM) and protein electrophoresis results were within normal limits. Abdominal ultrasonography (USG) revealed hepatomegaly (172 mm), coarse and heterogeneous liver echogenicities, a dilated portal vein (14 mm), and splenomegaly (140 mm). Ferritin, ceruloplasmin, serum copper, and α_1-antitrypsin levels were within normal ranges. Kaiser-Fleischer ring was not detected. Neurologic examination and cranial magnetic resonance imaging (MRI) findings were normal. The urinary copper excretion was within the normal range. Because the patient had a history of long-term ornidazole use and no other aetiological factors, we diagnosed ornidazole-induced hepatitis.

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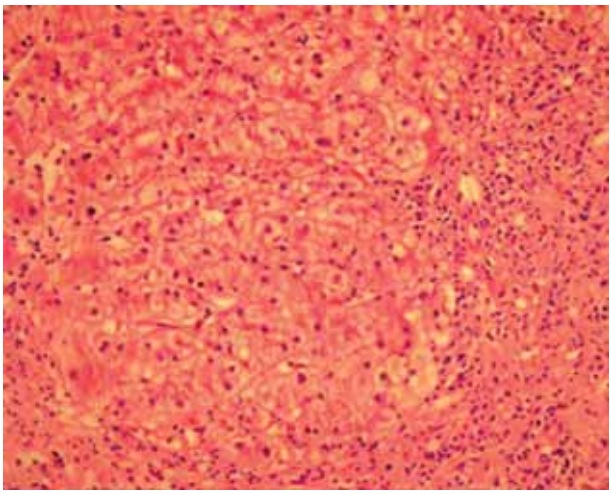

Fig. 1. — The portal tracts were moderately expanded and infiltrated by lymphocytes, eosinophils, plasmocytes, and neutrophils. Parenchymal cells showed cholestasis and feathery degeneration (HE × 200).

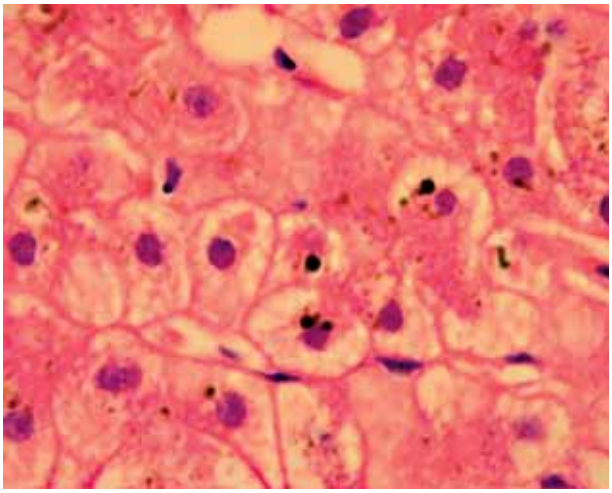

Fig. 2. — Hepatocanalicular bile stasis (HE × 1000-immersion oil).

We did not recommend any specific treatment except bed rest. During the follow-up period, the levels of serum transaminases decreased (ALT 232 and AST 108), but the level of total bilirubin increased (44.0 mg/dl). Therefore, we performed a percutaneous liver biopsy. Histopathologic examination revealed moderate portal inflammation with lymphocytes, eosinophils, plasma cells, and neutrophils (Fig. 1), inflammation of bile ductules with lymphocytes and neutrophils, diffuse degenerative changes in the bile duct cells, diffuse severe ballooning, giant cell formation, cholestatic degeneration in the hepatocytes, hepatocellular and canalicular cholestasis (Fig. 2), porto-portal and porto-central bridging fibrosis (stage 4-5/6), and a tendency to nodular formation (Fig. 3). These findings suggested a drug-induced severe hepatitis.

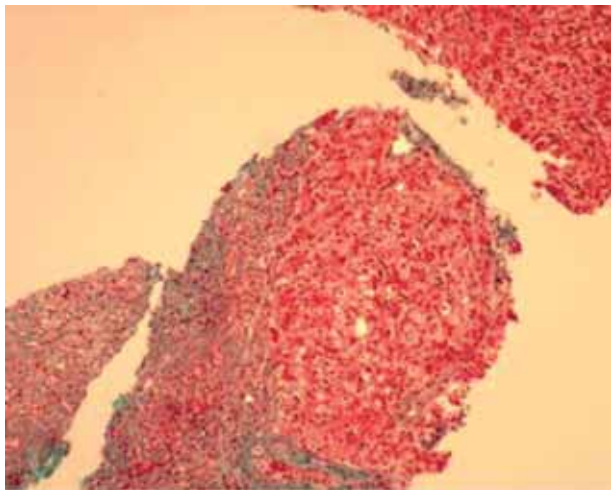

Fig. 3. — Portal fibrous expansion, porto-portal bridging fibrosis, and a tendency to nodular formation (Masson – Trichrome × 100).

Because there were findings consistent with splenomegaly and a dilated portal vein on the upper abdominal ultrasonographic examination, we performed esophagogastroduodenoscopy. This examination revealed portal gastropathy (mosaic-like pattern) and mild marked esophageal veins. Dynamic liver computerized tomography showed hepatosplenomegaly and perihepatic and perisplenic ascites. Portal color Doppler ultrasonography revealed hepatosplenomegaly, a dilated portal vein (14 mm), and the portal vein blood flow pattern was normal. During a follow-up after 8 weeks in the hospital, the total bilirubin level had decreased to 35.2 mg/dl. The patient had no complaints and was discharged in January 2006. The serum transaminase and total bilirubin levels were followed monthly. Although the serum transaminase levels did not change significantly, the total bilirubin levels gradually decreased after 1 month (Table 1). In the last clinical examination, the patient was in good health and jaundice had disappeared. Abdominal USG revealed irregular liver margins, persistent heterogeneous liver echogenicity, and hepatosplenomegaly. The laboratory results were as follows : ALT, 144 U/l ; AST, 128 U/l ; total bilirubin, 1.6 mg/dl ; and prothrombin time, 14.0 seconds.

Discussion

We present a female patient who developed hepatitis with accompanying deep jaundice. The patient was living in an area where amoebiasis was endemic and had a history of long-term ornidazole use (8 weeks) for resistant intestinal amoebiasis.

Although many drugs, such as nitrofurantoin, methyldopa, naproxen, and diclofenac, are well known to lead to liver injury (5) , there is very limited data about nitroimidazole derivative-induced liver injury. Kosar *et al.* (7) reported that ornidazole use triggered

Table 1. — **Serum transaminases (AST and ALT), total bilirubin, albumin, and prothrombin time values before ornidazole use and in the follow-up period after ornidazole use**

	AST (U/l)	ALT (U/l)	Total bilirubin (mg/dl)	Albumin (g/dl)	Prothrombin time (seconds)
Before ornidazole	17	15	1.5	4.0	14.5
After ornidazole					
1 month	2434	1593	28.6	3.5	25.4
2 months	232	108	44.0	3.3	15
3 months	269	88	35.2	3.0	14.6
4 months	156	84	8.9	3.2	14.7
5 months	128	144	1.6	3.8	14.0

autoimmune hepatitis in a 35-year-old female patient, who was treated successfully with corticosteroids. Ersoz *et al.* (6) reported that the use of nitroimidazole derivatives (metronidazole and ornidazole) at different times led to chronic hepatitis in a 36-year-old female patient. Tabak *et al.* (8) reported that ornidazole use led to cytolytic and cholestatic liver injury in three middle-aged female patients. Our patient developed liver injury after the longest duration (8 weeks) of ornidazole use reported in the literature. She was a middle-aged female, similar in age to the other patients described. Her autoimmune markers were negative, as with the other patients, except the patient reported in the Kosar *et al.* study (7). We investigated all aetiologic factors (alcohol, viral, and metabolic) that are known to be causal for chronic liver disease, but we did not detect any possible aetiological factors. Therefore, we decided that our patient had severe hepatitis with prolonged cholestasis and bile duct injury due to the long-term use of ornidazole. The liver biopsy revealed hepatocellular and canalicular cholestasis, portal inflammation, porto-portal and porto-central bridging fibrosis, and a tendency to nodular formation (stages 4-5/6). The abdominal USG findings, such as irregular liver margins, persistent heterogeneous echogenicity, and splenomegaly, were compatible with chronic liver disease. The serum transaminases levels had not returned to normal at the last laboratory examination, 5 months after the onset of clinical hepatitis. All these findings show that long-term ornidazole use may lead to serious liver damage.

In conclusion, nitroimidazole derivatives have been used worldwide for amoebiasis, genitourinary tract infections, and anaerobic infections. The clinical, laboratory, and imaging features of those cases reported in the literature who developed liver injury following use of nitroimidazole derivatives, especially females, indicate that these drugs may cause severe liver injury.

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