Ornidazole-induced hepatitis

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To the Editor,

Ornidazole, a synthetic nitroimidazole derivative, is a commonly prescribed antiparasitic drug for parasitic infestations, including amoebiasis, giardiasis and *Trichomonas vaginalis*. The drug is generally well tolerated. Hepatobiliary dysfunction associated with ornidazole has been reported infrequently (1-4). Here, we describe a Turkish female patient who developed hepatitis after ornidazole use.

A 57-year-old woman was diagnosed as having vaginitis and was prescribed ornidazole (1 g/day) for 10 days. One week after ornidazole discontinuation she complained of dark urine and jaundice and presented at her local hospital. Laboratory investigation showed total bilirubin 6.62 mg/dL, (N < 1.2 mg/dL) conjugated bilirubin 4.5 mg/dL, aspartate aminotransferase (AST) 1310 U/L (N < 37 U/L), alanine aminotransferase (ALT) 1633 U/L (N < 40 U/L) gamma glutamyltransferase (GGT) 183 U/L, (N < 85 U/L) anti-HAV IgM negative, HBsAg negative, anti-HBs negative, anti-HCV negative, HCV RNA negative and prothrombin time was normal. The upper abdominal ultrasound did not show any abnormality. She was given no medication.

Two weeks later, she was admitted to our hospital although the symptoms of dark urine and jaundice had almost fully resolved. Physical examination revealed only mild scleral jaundice, but no stigmata of chronic liver disease. She had no history of allergic reactions, liver disease, risk factors for viral hepatitis, alcohol use, or hematological disorders, and no recent history compatible with acute hypotension or having underlying heart disease. ALT and total bilirubin were decreased to 513 U/L and 3.05 mg/dL respectively, but alkaline phosphatase (ALP) was elevated at 459 U/L (N < 270 U/L). White cell count, hemoglobin and platelet count were within the normal range. Differential white cell count showed no eosinophilia. Repeated serologic tests for viral hepatitis were all negative except for anti-hepatitis A IgG. Tests for acute cytomegalovirus or Epstein-Barr virus infections were negative. Serologic markers for auto-immune hepatitis, anti-nuclear antibodies, antibodies to mitochondria, microsomes, smooth muscle or soluble liver antigen/liver pancreas, were all negative. She was given no medication. Three weeks later (6 weeks after ornidazole discontinuation) total bilirubin and GGT levels returned to normal ; ALT and ALP were reduced to near-normal levels. Finally, 10 weeks after ornidazole discontinuation ALT returned to normal as well, but ALP remained slightly elevated. The patient's liver function tests obtained during the course of hepatitis were shown in Table 1. Use of the Naranjo scale and Council for International Organizations of Medical Sciences/ Roussel Uclaf Causality Assessment Method (CIOMS/ RUCAM) scale, both indicated a probable relationship between ornidazole and hepatitis in this patient.

Metronidazole and ornidazole, synthetic nitroimidazole derivatives, are commonly used in the treatment of protozoal and anaerobic infections, and reports of hepatotoxicity are rare. According to the review by Tabak *et al*, there were 9 cases of hepatotoxicity related to nitroimidazole derivatives by 2002 (4). To our knowledge, one additional case in which the patient showed cholestasis and bile duct injury due to ornidazole treatment has been reported since 2002 (2).

Patients with drug-induced hepatitis may have cytolitic, cholestatic or mixed liver injury. In the report by Tabak *et al.* in which three cases of ornidazole-induced hepatitis were studied, liver histology of one patient revealed apparent cholestasis whereas there was mild cholestasis with apparent hepatocellular necrosis in histology of two other cases (4). Although a liver biopsy could not be performed to elucidate the type of liver injury, our case showed both cholestatic and cytolytic liver injury according to CIOMS classification as R value was calculated as 2.9. CIOMS/RUCAM score of 7 indicated a probable association between ornidazole and drug-induced hepatitis in our patient. Ornidazole may trigger an auto-immune hepatitis as previously described by Kosar *et al.* (3). Their patient developed an auto-immune hepatitis after ornidazole use and was managed successfully by corticosteroids. All three patients reported by Tabak *et al.* recovered within 4-7 weeks after drug discontinuation without any intervention. Tabak and co-workers noted that symptoms of the first case developed

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Table 1. — **Liver function test values during follow-up**

Parameters	Weeks after ornidazole discontinuation			
	1*	**3**	**6**	**10**
AST (< 37 U/L)	1310	255	37	18
ALT (< 40 U/L)	1633	513	42	16
ALP(< 110 U/L)		459	295	290
GGT (< 85 U/L)	183	175	67	29
Total bilirubin (< 1.2 mg/dL)	6.62	3.05	1.05	0.51
Albumin (g/dL)		4.4	4.3	3.8

* Results of tests performed at a distinct hospital. ALP = alkaline phosphatase ; ALT = alanine aminotransferase ; AST = aspartate aminotransferase ; GGT = gamma glutamyltransferase ; PT = prothrombin time.

at the second course of ornidozole treatment. For the second and third case, symptoms developed respectively 10 and 15 days after treatment discontinuation (4). In our case, symptoms began 1 week after drug withdrawal, and almost fully recovered within 6 weeks. With respect to those characteristics (temporal relationship and recovery period), our case is consistent with previous cases of Tabak *et al.* (4).

In conclusion, ornidazole, a frequently used nitroimidazole derivative, may cause hepatotoxic damage. Early recognition is mandatory and withdrawal of the drug may prevent further damage.

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