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Hepatitis induced by nomifensine

Nomifensine is an antidepressant that is being increasingly prescribed because of its relative lack of cardiovascular and anticholinergic side effects. We report a case of severe hepatitis due to a hypersensitivity reaction to nomifensine.

Case report

A woman aged 67 was admitted to hospital because of depression and difficult social circumstances. She had no history of alcoholism. On examination she looked depressed and had a blood pressure of 220/120 mm Hg but was otherwise normal. All laboratory investigations, including liver function tests, gave normal results. Chest radiography and electrocardiography showed left ventricular hypertrophy. Her hypertension was controlled with nifedipine retard 20 mg twice daily, and she was given nomifensine 25 mg four times a day for depression.

Four weeks later she developed jaundice associated with loss of appetite, general malaise, and muscle pains. She was afebrile, her liver and spleen were not palpable, and there was no ascites. Laboratory investigations showed: haemoglobin concentration 13.2 g/dl, mean cell volume 83 fl, white cell count $7.8 \times 10^9/l$ with 35% eosinophils, erythrocyte sedimentation rate 30 mm in the first hour, total serum bilirubin concentration 250 $\mu\text{mol/l}$ (14.6 mg/100 ml), alkaline phosphatase activity 455 IU/l, and total protein γ -glutamyl-transferase activity 243 IU/l. Abdominal ultrasound examination showed some gall stones but no dilated bile ducts. Immunological screening, including tests for antinuclear factor, smooth muscle antibodies, and anti-mitochondrial antibodies, a direct Coombs' test, and tests for hepatitis A and B gave negative results. Serum IgG concentration was 21.2 g/l, but serum concentrations of other immunoglobulins, C3, and C4 were within normal limits.

A percutaneous liver biopsy (figure (top)) showed bridging (periacinar) necrosis, collapsed reticulin framework, central veins linked with portal tracts and each other, pseudolobules, centrilobular cholestasis, and bile plugs. The portal tracts were oedematous and infiltrated with lymphocytes, plasma cells, polymorphonuclear leucocytes, and eosinophils. Bile duct proliferation and acute cholangitis were also seen. There was no evidence of cirrhosis.

Drug induced hepatitis was diagnosed and nifedipine and nomifensine stopped. Her jaundice and blood eosinophilia resolved in the following eight weeks. Results of liver function tests had returned to normal after 14 weeks. A repeat liver biopsy 16 weeks after the onset of jaundice showed normal liver architecture (figure (bottom)) with no evidence of bridging necrosis or cholestasis. The portal areas showed fibrosis with infiltration of a few lymphocytes, plasma cells, and eosinophils. Bile duct proliferation was present but there was no cholangitis. Nomifensine was thought to be the more likely cause of the hepatitis, which had not recurred three months after nifedipine retard was reintroduced for hypertension.

Comment

The four week interval between the start of treatment and the appearance of jaundice, blood and tissue eosinophilia, and hepatitis similar to viral hepatitis but with no demonstrable viral infection or autoimmune disease suggested a drug induced hypersensitivity reaction.¹

Early clinical trials with nomifensine showed mild and transient abnormalities of liver function in a small proportion of patients. Since the drug's introduction in the United Kingdom there have been some reports of hepatotoxic reactions, but only a few seemed to be definitely

Liver biopsy specimen showing (top) bridging necrosis, pseudolobules, and portal tract infiltrated by lymphocytes, plasma cells, and eosinophils (haematoxylin and eosin $\times 125$); (bottom) normal architecture with no evidence of bridging necrosis, pseudolobules, or cholestasis. Portal tract shows fibrosis with infiltration of a few lymphocytes, plasma cells, and eosinophils (haematoxylin and eosin $\times 250$) (original magnifications).

correlated with the drug (J Kranse, Albert Products, personal communication). Nomifensine has been reported to cause hepatic epithelioid cell granulomas that resolved after it was stopped.² In another case nomifensine produced clinical and histological features of mild hepatitis similar to viral hepatitis, but with no loss of liver architecture, which recurred after reintroduction of the drug.³ In our patient the hepatic injury was more severe.

Drug induced hypersensitivity reactions are rare and unpredictable. Nomifensine has been reported to cause immune haemolytic anaemia with renal impairment,⁴ but this is the first report to our knowledge of hepatitis caused by hypersensitivity to nomifensine. We have reported this case to the Committee on Safety of Medicines.

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