

Alverine induced toxic hepatitis: A case report

Alverine baęlı toksik hepatit: Olgu sunumu

Ziyaettin DURAKOęLU, Güngör BOZTAŞ, Ali SEZGİL, Sabahattin KAYMAKOęLU, Dinç DİNÇER, Sadakat ÖZDİL, Fatih BEŞİŞİK, Zeynel MUNGAN, Atilla ÖKTEN

Istanbul University, Istanbul Medical Faculty, Department of Gastroenterohepatology Çapa, İstanbul

Drug-induced hepatotoxicity is an important cause of hepatocellular injury. Hepatic necrosis may range from asymptomatic elevations in transaminases to fulminant hepatic failure and death. Alverine is an antispasmodic drug which is especially used in patients with irritable bowel syndrome. Only a few cases of alverine associated hepatotoxicity have been reported previously. We present the case of a patient with alverine induced hepatotoxicity and cholestasis, which has only seldomly been reported in the literature.

Keywords: Alverine, hepatotoxicity.

İlaca baęlı hepatotoksisite hepatosellüler hasarın önemli nedenlerinden biridir. Hepatik nekroz hafif transaminaz yükseliklerinden fulminan hepatite ve ölüme kadar deęişen derecelerde olabilir. Alverine, özellikle iritabl barsak sendromu olan hastalarda anti-spazmodik olarak kullanılmaktadır. Alverine'e baęlı hepatotoksisite çok nadir bildirilmiştir. Alverine'e baęlı akut hepatit ve kolestazla seyreden toksik hepatit olgumuz, literatürde bu tür vakaların çok nadir olması nedeni ile ilginç bulunarak sunulmuştur.

Anahtar sözcükler: Alverine, hepatotoksisite.

INTRODUCTION

Drug-induced hepatotoxicity is an important cause of hepatocellular injury and hepatic necrosis may range from asymptomatic elevations in transaminases to fulminant hepatic failure and death (1,2). Alverine, an antispasmodic drug which is especially used by patients with irritable bowel syndrome, is almost totally absorbed through the gastrointestinal tract and is mainly metabolised by the liver, with only a small amount being excreted excreted by the kidneys. Only a few alverine associated hepatotoxicity cases have been reported previously (3).

The detection of autoantibodies in serum is one finding of drug induced hepatitis (4). However, autoantibodies have been detected in toxic hepatitis particularly due to oxyphenisatin, alpha methyl dopa and nitrofurantoin (5-7) in only one patient to date (3).

The following case is presented because the clinical picture of acute hepatitis and cholestasis associated with alverine is rarely seen.

CASE

A 54-year old female was admitted to our clinic with a history of weakness, pruritis, jaundice and dark-colored of urine, beginning on the seventh day of alverine therapy which she had been taking for four months for a diagnosis of functional constipation. Her medical history included only appendectomy at 16 years of age. Physical examination showed that she was conscious, icteric and had 2 cm hepatomegaly. Hematologic and blood chemical values were as follows: Erythrocyte sedimentation rate 38mm/h, leucocyte 10060/mm³, hematocrit 39.9%, hemoglobin 12.6 g/dL, platelet 357000/mm³, AST 431U/L (5-42), ALT 684U/L (5-45), ALP 316U/L (90-260), GGT 205 U/L (5-85), total bilirubin 6.52 mg/dL, direct bilirubin 5.4 mg/dL, albumin 3.7 g/dl, gamma globulin 1.77 g/dL. Urinalysis revealed (+++++) bilirubin and (++) urobilinogen. Viral serologic markers were as follows: Anti HAV-IgM negative, HBsAg negative, Anti HBc IgM negative, Anti HBs positive, Anti HCV negative, IgM and IgG antibodies to CMV, EBV and HSV negative. ANA, AMA and M2 were

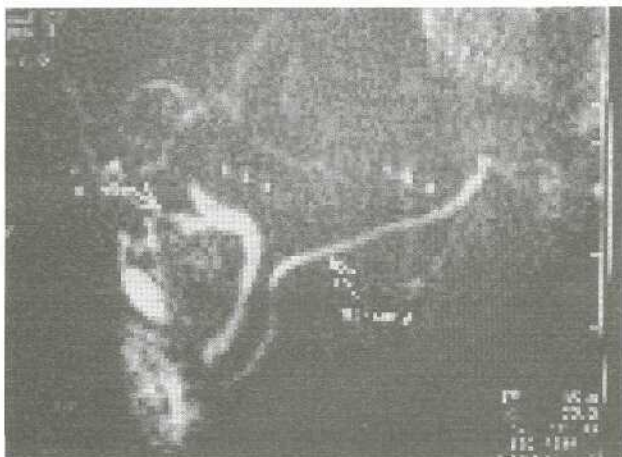


Figure 1. MRCP disclosed no pathology.

negative, while anti smooth muscle antibody (ASMA) was detected positively at a titer of 1/40. Ultrasonography (USG) showed normal liver structure, intrahepatic bile ducts and normal gall bladder. Magnetic resonance cholangio pancreatography (MRCP) (Figure 1) and endoscopic retrograde cholangiopancreatography (ERCP) disclosed no pathology. Liver biopsy showed sparse hydropic and granular degeneration of the hepatocytes, diffuse and moderate bile accumulation and a bile thrombus in the hepatocytes and canaliculus, Kupffer cell hyperplasia, focal necrosis, endothelitis of the vena centralis with sparse lymphocyte and neutrophils and mild portal infiltration with mononuclear cells and esinophils (Figure 2). Evaluation of clinical, laboratory and histopathologic examination, was in favor of the diagnosis of toxic hepatitis. The diagnosis was established after exclusion of autoimmune and extrahepatic causes, and alverine therapy was then stopped.

Oral therapy of rifampicin 300mg/day and loratadine 10mg/day was commenced due to severe pruritis. The patient improved rapidly with complete resolution of symptoms and normal laboratory values within two months of initiation of treatment. Recovery following alverine discontinuation and a negative result of re-checked ASMA confirmed the diagnosis of alverine associated toxic hepatitis presenting with cholestasis.

DISCUSSION

This patient was diagnosed with alverine induced

toxic hepatitis according to the criteria of 1988 Consensus Meetings (8). There was no history of liver and biliary disease or alcohol consumption in the patient and serological markers of viral hepatitis were negative. Antimitochondrial antibody for primary biliary cirrhosis was also negative, while ASMA became negative after alverine discontinuation. Ultrasonography, MRCP and ERCP showed no biliary disease. The absence of systemic (including autoimmune ones) disease findings, tumoral infiltration of liver disease, and no history of hypotension or heart disease excluded other diseases affecting the liver. There was no history of other drug use. Histological findings were concordant with toxic hepatitis. The case was diagnosed with toxic hepatitis following evaluation of all these criteria.

Alverine is a drug that has papaverine-like effects but is chemically different from papaverine. Both acute and chronic toxic effects have been reported following papaverine therapy and the mechanism of its toxicity was found to be connected with immunity (9). In the literature, the first reported case of alverine induced hepatotoxicity proved the existence of esinophils in the liver and positivity of lamin A and C class autoantibodies, which supported the theory that this toxicity was related to immunity. In this patient, anti lamin A and C had been become negative 100 days following drug discontinuation (3). In our case, The ini-

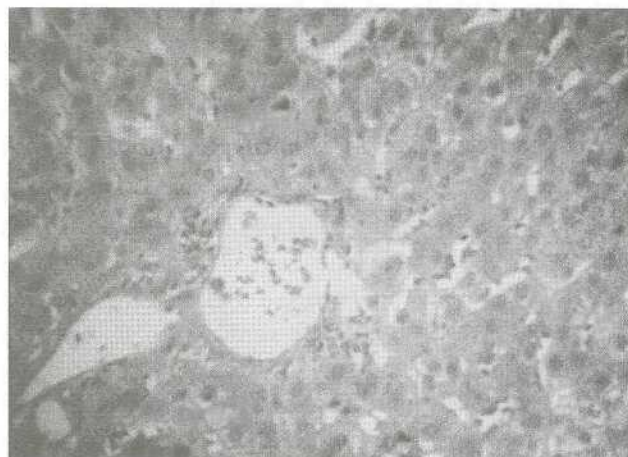


Figure 2. Liver biopsy of case (Hydropic and granular degeneration of hepatocytes, diffuse and moderate bile accumulation and bile thrombus in hepatocytes and canaliculus, Kupffer cell hyperplasia, focal necrosis, endothelitis of vena centralis with sparse lymphocyte and neutrophil, mild portal infiltration with mononuclear cells and esinophils) (H&EX400).

tal positive test of ASMA at a titer of 1/40 became negative within two months of alverine discontinuation. The histological findings were similar to

that of cellular rejection. These histological findings and ASMA positivity suggest an immunological basis for this toxicity.

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