

Alverine citrate induced acute hepatitis

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Abstract

Alverine citrate is a commonly used smooth muscle relaxant agent. A MEDLINE search on January 2004 revealed only 1 report implicating the hepatotoxicity of this agent. A 34-year-old woman was investigated because of the finding of elevated liver function tests on biochemical screening. Other etiologies of hepatitis were appropriately ruled out and elevated enzymes were ascribed to alverine citrate treatment. Although alverine citrate hepatotoxicity was related to an immune mechanism in the first case, several features such as absence of predictable dose-dependent toxicity of alverine citrate in a previous study and absence of hypersensitivity manifestations in our patient are suggestive of a metabolic type of idiosyncratic toxicity.

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INTRODUCTION

Toxic hepatitis is a liver injury caused by drugs and chemicals. The severity varies from nonspecific changes in liver functions such as abnormalities in liver enzymes to fulminant hepatic failure and cirrhosis. Its incidence has been increased over the past several decades. Drugs have been estimated to be responsible for 15-20% of all cases of fulminant and subfulminant hepatitis in Western countries and 18% of acute liver failure in the United States^[1,2].

Alverine citrate is a smooth muscle relaxant agent, commonly used in patients with irritable bowel syndrome in association with simethicone. Hepatotoxicity of alverine citrate is extremely rare and has been reported only in 1 patient before^[3]. Herein we report a new case of alverine citrate-induced hepatotoxicity occurred in a middle-aged woman that resolved completely after discontinuation of the drug.

CASE REPORT

On July 24, 2003, a 34-year-old woman was admitted to the Outpatient Clinic of Gastroenterology Department of Yuksek Ihtisas Hospital with the chief complaint of dyspepsia lasting for 2 years. She described bloating after meals and sometimes had gastroesophageal reflux symptoms. She did not have any chronic disease states. Physical examination was completely normal. Her biochemical tests including liver enzymes (AST, ALT, ALP and GGT) were all within normal limits. Upper

gastrointestinal endoscopy was performed showing grade I esophagitis and pangastritis. On July 29, omeprazole PO 20 mg bid, liquid alginic acid (Gaviscon) PO 10 mL qid (30 min after meal and at bedtime) and meteospasmyl (a tablet containing 60 mg alverine citrate and 300 mg simethicone) PO tid (before meals) were prescribed. Till the 14th d after prescription she told that she used all of the drugs as recommended. At that time omeprazole was ceased and she continued to medical treatment with Gaviscon and meteospasmyl.

She was admitted to another hospital because of arthralgia lasting for years on August 18, 2003, but therapy was managed on an outpatient basis. Amitriptyline 25 mg PO bid was added to Gaviscon and Meteospasmyl and a gastroenterology consultation was requested because of the finding of abnormal liver function test values on biochemical screening. On August 18, serum liver enzymes were as follows: ALT: 319 IU/L, AST: 211 IU/L (N: 40 IU/L for both); ALP: 184 IU/L (N: 35-129), GGT: 116 IU/L (N: 5-40) and normal direct and indirect bilirubin levels. She began to take amitriptyline on August 23 and readmitted to our hospital on August 26. Her ALT and AST levels were 1 119 IU/L and 853 IU/L, respectively. Other biochemical tests such as, hemoglobin level, white blood cell count, platelet count, and prothrombin time were within normal limits. Hepatobiliary imaging with ultrasonography was normal. Viral markers for hepatitis including hepatitis A, B and C viruses, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus were all negative. Autoantibodies (antinuclear, antimitochondrial, anti-smooth-muscle, anti-liver-kidney microsomal enzymes and anti-soluble liver antigen) were also negative. She denied taking any other medications and using alcohol or any herbal and folk remedies anytime. There were no known environmental issues that could be contributing.

Liver enzyme elevations were thought to be drug induced. Amitriptyline, Gaviscon and Meteospasmyl were all immediately discontinued on August 26. The ALT and AST values decreased to 597 IU/L and 237 IU/L 8 d after withdrawal of all drugs and became completely normal 18 d after cessation. The time course of liver function tests is presented in Table 1. Liver biopsy was not performed, and rechallenge with Meteospasmyl was not attempted because of ethical reasons. Since she had continuing mild symptoms related to gastroesophageal reflux, she continued to take Gaviscon and omeprazole without any increase in biochemical parameters.

Table 1 Time course of liver function tests

Date	AST (IU/L)	ALT (IU/L)	GGT (IU/L)	ALP (IU/L)
7/24/2003	30	32	21	162
8/18	211	319	116	184
8/26	853	1 119	-	-
9/3	237	597	-	229
10/2	22	21	35	75

Omeprazole, alginic acid, and alverine citrate were started on 7/30/2003. Omeprazole was ceased on 8/10/2003. Amitriptyline was added to alginic acid and alverine citrate on 8/23/2003 and all medications were discontinued on 8/26/2003. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ -glutamyl transferase.

DISCUSSION

Meteospasmyl is a most widely used drug for irritable bowel syndrome. It contains 60 mg alverine citrate and 300 mg simethicone. Simethicone has been used as an antifoaming agent and considered as an inert one^[4]. It is excreted via feces without any metabolizing in the gastrointestinal system. It has been widely used in patients with gastrointestinal gas and for the improvement of visibility during radiologic examination^[5]. To our knowledge, no systemic side effect regarding simethicone was reported in the literature.

Alverine is one of the papaverine congeners. Its antispasmodic effects are mediated by processes involving smooth muscle cells, extrinsic nervous system, and calcium channels^[6]. In humans, the drug is completely absorbed by the gastrointestinal tract and mainly metabolized in the liver, with negligible amounts excreted in the urine^[3]. Side effects such as flushing on the face and neck, nausea, headache, dizziness, and allergic skin eruptions may be observed. To our knowledge, hepatotoxicity associated with alverine use was reported once in the literature. Hepatotoxicity was not reported for the other papaverine derivatives other than trimebutine^[7].

In our patient increase in liver enzymes was ascribed to alverine treatment due to several reasons. There was a temporal relationship between alverine treatment and hepatitis. Liver function tests were normal before treatment and increases appeared three weeks after the start of alverine treatment. The timeline of exposure to alverine and initial observation of increase in liver function tests were consistent with drug-induced liver disease^[8]. Liver function tests completely normalized three weeks after withdrawal of the drug. Furthermore other etiologies of hepatitis (alcohol, steatohepatitis, autoimmune hepatitis and viral hepatitis) were appropriately ruled out. Omeprazole was not thought to be responsible for our patient's hepatitis in view of her prior uses of this drug without adverse effects. Neither chemical nor clinical side effects were seen in her consequent follow-up after alginic acid and omeprazole were started again. We therefore classified our case as probable alverine-induced hepatotoxicity according to the Naranjo probability scale^[9].

Drugs cause liver injury either via intrinsic toxicity (dose-dependent or predictable) or host idiosyncrasy (dose-independent or unpredictable). Idiosyncratic hepatotoxicity may be in metabolic or immunoallergic form. Metabolic-type idiosyncratic injury develops as a result of the susceptibility of rare individuals to hepatotoxicity from a drug that is usually safe at conventional doses. In this pattern, reactions would occur among susceptible individuals who possess an isolated genetic enzymatic alteration not expressed under normal conditions, which would become clinically apparent following the

administration of certain drugs^[10]. The mechanism of alverine induced liver disease is unknown. In the first case described in the literature alverine hepatotoxicity was related to immune mechanisms due to the presence of transient hypereosinophilia, eosinophil polymorphonuclear cells in the liver inflammatory infiltrates, and antinuclear autoantibodies. In our patient autoantibodies were negative and there was no hypereosinophilia in the peripheral blood smear. Several features such as the absence of predictable dose-dependent toxicity of alverine and fever, rash, and arthralgia (hypersensitivity manifestations) in our patient were consistent with a metabolic type of idiosyncratic toxicity.

In conclusion, alverine is a smooth muscle relaxant drug. This report presents the second case of alverine-associated possible liver toxicity. Alverine citrate should be included in the list of drugs causing toxic hepatitis.

REFERENCES

- 1 **Bernuau J**, Benhamou JP. Fulminant and subfulminant liver failure. In: Bircher J, Benhamou JP, McIntyre N, Rizzetto M, Rodes J, eds. *Oxford Textbook of Clinical Hepatology*, 2nd ed. Oxford: Oxford University Press 1999: 1341-1372
- 2 **Ostapowicz G**, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hyman L, Crippin JS, Blei AT, Samuel G, Reisch J, Lee WM. U.S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002; **137**: 947-954
- 3 **Malka D**, Pham B, Courvalin JC, Corbic M, Pessayre D, Erlinger S. Acute hepatitis caused by alverine associated with anti-lamin A and C autoantibodies. *J Hepatol* 1997; **27**: 399-403
- 4 **Brecevic L**, Bosan KI, Strajnar F. Mechanism of antifoaming action of simethicone. *J Appl Toxicol* 1994; **14**: 207-211
- 5 **Sudduth RH**, DeAngelis S, Sherman KE, McNally PR. The effectiveness of simethicone in improving visibility during colonoscopy when given with a sodium phosphate solution: a double-blind randomized study. *Gastrointest Endosc* 1995; **42**: 413-415
- 6 **Lemann M**, Coffin B, Chollet R, Jian R. Gut sensitivity: methodology for study in man and pathophysiological implications. *Gastroenterol Clin Biol* 1995; **19**: 270-281
- 7 **Bacq Y**, Vaillant L, Moneqier du Sorbier C. Severe erythema multiforme and hepatitis during treatment with trimebutine. *Gastroenterol Clin Biol* 1989; **13**: 522-523
- 8 **Lewis JH**. Drug-induced liver disease. *Med Clin of North Am* 2000; **84**: 1275-1311
- 9 **Naranjo CA**, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239-245
- 10 **Farrell GC**. Liver disease caused by drugs, anesthetics, and toxins. In: Feldman M, Scharschmidt BF, Sleisenger MH, eds. *Sleisenger and Fordtran's gastrointestinal and liver disease*. 6th ed. Philadelphia: W.B. Saunders Company 1998: 1221-1253

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