



CASE REPORT

Adverse hepatic reactions associated with calcium carbimide and disulfiram therapy: Is there still a role for these drugs?

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Supported by a research grant from the Agencia Española del Medicamento and a FIS grant, No.041688

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Received: 2006-03-06

Accepted: 2006-03-27

Abstract

Disulfiram and calcium carbimide are two alcohol deterrents widely used in alcoholism treatment, however, there exist great concerns over their safety. Reports on hepatotoxicity, mainly related to disulfiram therapy, have been published. The hepatotoxic potential of calcium carbimide is less well characterized. Here, we describe four cases of liver damage related to this therapeutic group that were submitted to a Registry of hepatotoxicity and point out the limitations that we face when prescribing these compounds. A reassessment of the role of these compounds in the management of alcohol dependence is clearly needed.

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Key words: Calcium carbimide; Disulfiram; Hepatotoxicity

Verge C, Lucena MI, López-Torres E, Puche-García MJ, Fraga E, Romero-Gomez M, Andrade RJ. Adverse hepatic reactions associated with calcium carbimide and disulfiram therapy: Is there still a role for these drugs? *World J Gastroenterol* 2006; 12(31): 5078-5080

<http://www.wjgnet.com/1007-9327/12/5078.asp>

INTRODUCTION

Disulfiram (tetraethylthiuram disulphide), an alcohol deterrent, is widely used in alcoholism treatment. Another

drug, calcium carbimide is less frequently prescribed and not on the market in many European countries, being commercialized in Australia, Canada, South Africa, Austria, Netherlands, Sweden and Spain, among others. These drugs produce physiological changes after ethanol consumption, which are sufficiently unpleasant to dissuade most alcoholics from further drinking. However, there exist great concerns over their safety. Both agents share a similar profile of adverse effects including dermatological and haematological reactions^[1]. Reports on hepatotoxicity, mainly related to disulfiram therapy and leading in some cases to fulminant liver failure, have been described^[2,3]. Indeed, in a recently published study by Björnsson & Ollson (2005) aimed to analyse the outcome of patients with severe drug-induced liver injury, disulfiram stood out as the second most commonly reported drug associated with mortality^[4]. Conversely, the hepatotoxic potential of the less prescribed calcium carbimide is not well recognized. We describe four cases of liver damage related to this therapeutic group that were submitted to a Registry of hepatotoxicity in work since 1994. The operational structure of the Registry, data recording and case ascertainment have been summarily reported elsewhere^[5]. Only cases considered drug-related by experts' clinical judgment were assessed by the Council for International Organizations of Medical Sciences scale (CIOMS scale)^[6], that provides a standardized scoring system according to the type of liver injury and based on six axes of decision-taking.

CASE REPORT

A 23-year-old man (patient 1) was prescribed calcium carbimide (120 mg/d) in July 1997. He was admitted to the hospital in August 1997 because of a week's history of fatigue, dark urine, and pruritus. Physical examination showed a pruriginous exanthema, marked jaundice, without any signs of chronic liver disease although he admitted an alcohol consumption of 80-100 g/d, and laboratory findings at presentation are shown in Table 1. Serology ruled out viral causes, screening for autoantibodies was negative and findings of an abdominal ultrasonographic examination were normal. A liver biopsy showed perivenular cholestasis and mild hepatobiliary damage. Liver tests were normal on 49 d after drug withdrawal. This case yielded 11 points when applying the CIOMS scale which fell into the category of highly probable.

A 39-year-old man (patient 2) on chronic alcohol con-

Table 1 Serum concentrations at time of presentation with calcium carbimide or disulfiram induced liver damage

Patient	Bilirubin (mg/L)		ALT (U/L)	AP (\times ULN)	Type of liver injury
	Total	Direct			
1	22.4	14.4	553	$\times 3.4$	Cholestatic hepatitis ¹
2	0.9	0.2	59	$\times 0.56$	PAS-positive ground glass hepatitis ¹
3	11.8	8.43	713	$\times 1.4$	Hepatocellular
4	27.1	16.72	1288	$\times 1.49$	Septal fibrosis and active Chronic hepatitis ¹

¹ Liver biopsy findings. Abbreviations: ALT, alanine aminotransferase ($n < 40$ U/L); AP, alkaline phosphatase; ULN, upper limit of normality; total bilirubin ($n < 1.2$ mg/dL). The ALT and AP values are these at presentation where as bilirubin values are the highest recorded.

sumption (110 g/d) was prescribed calcium carbimide (75 mg/d) for aversion therapy in February 1995. After 25 wk of treatment he was admitted to hospital because of an increase in serum transaminases, with a ratio of alanine aspartate and alanine aminotransferase of 1.05 (62/59, UL) (Table 1). The patient admitted alcohol abstinence for the previous 6 mo and during the course of the medical treatment. Physical examination disclosed hepatomegaly without any signs of chronic liver disease. Serology tests ruled out viral causes. Screening for autoantibodies produced negative results, and the results of an abdominal ultrasonographic examination were normal. A liver biopsy elicited ground-glass inclusion bodies in the hepatocytes associated with portal inflammation and fibrosis. The patient did not attend any further appointments.

A 42-year-old woman (patient 3) was prescribed venlafaxine (75 mg/d) and alprazolam (1.5 mg/d) for depression, and calcium carbimide (75 mg/d) since December 2002. Mean daily alcohol ingestion was 120 g/d that was stopped 45 d prior to admission. The results of prior liver function tests were normal. After 75 d of treatment she was admitted to hospital because of asthenia and fever, and a diagnosis of spontaneous bacterial peritonitis was made. Physical examination showed a jaundiced patient without stigmata of chronic liver disease. Serum chemistry indicated hepatocellular injury (Table 1) without evidence of viral causes. Over the next days she developed fulminant hepatic failure unresponsive to molecular adsorbent recirculating system (MARS) therapy which was unsuccessfully instituted three times and died on d 31 after hospitalization. This case yielded 6 points when applying the CIOMS scales which fell into the category of probable.

A 48-year-old man (patient 4) was admitted to hospital in August 2003 because of a five-day history of fatigue and dark urine one month after automedication with disulfiram (1000 mg/d). He had been taking phenytoin 200 mg/d for epilepsy for 5 years. He was a heavy alcohol drinker (> 80 g/d) and although he denied alcohol intake in the previous month he was actually an active consumer. Physical examination showed marked jaundice with signs of chronic liver disease. Serum chemistry indicated hepatocellular injury (Table 1). Screening for viral disease was negative and abdominal ultrasonographic examination

showed normal biliary ducts and moderate ascites. Liver biopsy revealed a chronic active hepatitis and septal fibrosis. Laboratory findings returned to previous baseline values 9 mo after drug withdrawal.

We described four cases of adverse liver reactions related to the use of calcium carbimide (3 cases) and disulfiram (1 case) because there was a temporal relationship between the administration of the drugs and the onset of hepatic abnormalities as well as between withdrawal of the drugs and improvement in liver dysfunction, the only exception being patient 3 who developed fulminant liver failure. In patient 2 de-challenge could not be ascertained because the patient was lost to follow up. Indeed, in this patient the increase in alanine aminotransferase was less than two times the upper limit of normal and since the biochemical expression of liver injury according to the International consensus criteria^[7] was a biological damage, causality assessment with the CIOMS scale was not performed. However, he presented in the liver specimen the hepatocyte inclusions seen only with calcium carbimide therapy along with fibrosis and lymphocyte portal inflammation characteristic of a chronic form of liver damage^[2,8].

On the other hand, causes of liver damage (viral, immunologic and metabolic) were ruled out. In patient 4, liver biopsy ruled out a diagnosis of alcoholic hepatitis. Patient 3 was prescribed venlafaxine which has been associated with non fatal cases of hepatotoxicity^[9].

The mechanism of aversion therapy-induced hepatotoxicity is presumed to be idiosyncratic. The absence of clinical features of hypersensitivity in these cases suggests that a toxic metabolite may be responsible, although an immune mechanism has been implicated in some cases^[3]. Both compounds are extensively metabolized in the liver and block the oxidation of alcohol at acetaldehyde stage increasing acetaldehyde blood levels. Therefore, their administration requires the agreement of the patient to stop drinking. In our series patient 4 self administered disulfiram while continuing drinking which could have rendered him at risk of severe medical complications. Furthermore, another concern related to the use of alcohol deterrents is the possibility of drug interactions. Actually, they may inhibit the metabolism of drugs such as phenytoin (CYP 2C19) and an interaction with the antidepressant venlafaxine cannot be discarded. Coadministration of aversive therapy with other drugs (antibiotics, amitriptyline, *etc.*) could aggravate/precipitate the disulfiram-alcohol reaction. It is not yet known whether associate medications might contribute to the hepatotoxic effect of these drugs^[1]. It is also important to highlight that since these compounds may be prescribed to patients with underlying alcoholic liver disease such as liver cirrhosis and alcoholic hepatitis (although they should be cautiously prescribed if at all in this population), the diagnosis of hepatotoxicity may go unrecognised.

In summary, these cases exemplify the main limitations of use that these two principal alcohol-sensitizing drugs present. Furthermore, since the efficacy of aversive therapy remains to be proved^[10], a reassessment of the role of these compounds in the management of alcohol dependence is clearly needed.

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S- Editor Wang J L- Editor Zhu LH E- Editor Ma WH