Thioctic Acid–Induced Acute Cholestatic Hepatitis

Ezequiel Ridruejo, Teresa Castiglioni, and Marcelo O Silva

OBJECTIVE: To report a case of severe cholestatic hepatitis caused by thioctic acid in a patient with diabetic peripheral polyneuropathy and mild chronic renal failure.

CASE SUMMARY: A 63-year-old man with type 2 diabetes, hypertension, hypothyroidism, and stage 2 chronic renal failure was referred to the outpatient liver clinic with fever, asthenia, nausea, and pruritus. Because of the presence of symptomatic diabetic neuropathy, he began treatment with thioctic acid 600 mg/day. Serum transaminase levels were measured before starting thioctic acid treatment and values were within the normal range. Symptoms progressively worsened and the patient developed a low-grade fever and evidence of increased serum liver enzyme levels 45 days after starting thioctic acid treatment: aspartate aminotransferase (AST) (114 IU/L [reference range <40]), alanine aminotransferase (ALT) (191 IU/L [<35]), alkaline phosphatase (ALP) (562 IU/L [<130]), and γ-glutamyltransferase (GGT) (592 IU/L [<50]). Thioctic acid treatment was discontinued 2 days after admission. Four months after the initial presentation, his AST, ALT, and ALP levels normalized and GGT level had decreased (88 IU/L). As the patient's neuropathic symptoms worsened, thioctic acid therapy was restarted. Two months after restarting therapy, pruritus, nausea, and asthenia reappeared and the patient's liver enzyme levels became clearly abnormal again (AST 100 IU/L, ALT 129 IU/L, ALP 161 IU/L, GGT 180 IU/L). Thioctic acid was stopped, and the patient's liver enzyme levels returned to normal 2 months later.

DISCUSSION: Alpha-lipoic acid, also known as thioctic acid, improves metabolic glucose control and peripheral neuropathies associated with diabetes mellitus. Its administration appears to be safe and, as far as we know, there are no reports of liver toxicity associated with its use. Our patient developed acute cholestatic hepatitis after beginning treatment with thioctic acid. Use of the Roussel Uclaf causality assessment scale indicated that the association between thioctic acid treatment and our patient's drug-induced liver injury was highly probable; use of the Maria and Victorino scale indicated that the association was probable.

CONCLUSIONS: To our knowledge, this is the first report of probable liver toxicity due to thioctic acid, a proposed "hepatoprotectant."

KEY WORDS: drug-induced liver injury, hepatotoxicity, thioctic acid.

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Alpha-lipoic acid, a naturally occurring dithiol compound, also known as thioctic acid, has long been known as an essential cofactor of mitochondrial bioenergetic enzymes. It is a very important micronutrient with diverse pharmacologic and antioxidant properties. Pharmacologically, thioctic acid improves metabolic glucose control and peripheral neuropathies associated with diabetes mellitus.[1,2] Its administration appears to be safe and, to our knowledge, there have been no reports of liver toxicity with its use.[3,4]

Case Report

A 63-year-old man with a history of type 2 diabetes, hypertension, hypothyroidism, and stage 2 chronic renal failure was referred to the outpatient liver clinic with fever, asthenia, nausea, and pruritus. Medication at the time of the initial visit consisted of subcutaneous insulin glargine, oral valsartan 160 mg/day, and levothyroxine 88 µg/day (he had been taking the valsartan and levothyroxine for more than 3 years). He began treatment of symptomatic diabetic neuropathy with thioctic acid 600 mg/day (Tiodrix HR, Merck Serono, Geneva, Switzerland) in December 2009, resulting in better control of the neuropathic symptoms. Serum aminotransferase levels were measured before starting thioctic acid treatment and values were within the normal range.

In February 2010, the patient experienced asthenia and nausea, and later developed pruritus. Symptoms progressively worsened and the patient developed a low-grade fever and evidence of increased serum liver enzyme levels 45 days after starting thioctic acid (Table 1). The patient had no risk factors for HIV or viral hepatitis and he reported no use of alcohol and herbal or alternative medicines. On March 10, the patient was admitted for further evaluation and potential treatment. Two days after admission, thioctic acid was discontinued. The initial complete blood

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and eosinophil counts were within normal limits, but serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ-glutamyltransferase (GGT) levels progressively increased. Serologic tests for HIV and viral hepatitis (cytomegalovirus; Epstein-Barr virus; and hepatitis A, B, C, and E virus), as well as serum antimitochondrial, antinuclear and anti–smooth muscle antibodies, were performed. Results of virologic and autoimmune tests were negative. Iron, copper, and thyroid hormone values were also within the normal range, and blood and urine cultures showed no microorganisms after 72 hours of inoculation. Abdominal ultrasound and computed tomography scan showed no liver or pancreatic masses. No intra- or extra-hepatic biliary tree obstructions were seen on magnetic resonance cholangiography. A liver biopsy was then performed and showed zone 3 parenchymal bilirubinostasis with an isolated necrotic hepatocyte focus surrounded by a minimal lymphocytic infiltrate. There was no bile duct damage, ductopenia, ductular proliferation, portal inflammation, or portal fibrosis (Figures 1 and 2). Results of Perls' Prussian blue, Congo red, periodic acid-Schiff, Grocott, and acid-fast stains were all negative.

Three days later, the patient's fever and nausea resolved without any specific treatment. Results of liver function tests improved, and the patient was discharged without a definitive diagnosis and followed at the liver clinic. In June, his liver enzyme levels, other than GGT, were normal. In early July, because of worsening neuropathic symptoms, thioctic acid therapy was restarted. Two months later, pruritus, nausea, and asthenia reappeared and liver enzyme levels became abnormal again (Table 1). Thioctic acid was stopped, and liver enzymes returned to normal levels 2 months later.

Discussion

The clinical course and laboratory data observed in this case are consistent with the diagnosis of cholestatic hepatitis probably due to thioctic acid. It fulfills all the criteria proposed by the Drug-Induced Liver Injury Network to assume a relationship between the drug and the adverse event.[5] Use of the Roussel Uclaf causality assessment scale indicated that the association between thioctic acid treatment and our patient's drug-induced liver injury was highly probable; use of the Maria and Victorino scale indicated that the association was probable.[6]

A wide spectrum of etiologies for our patient's liver disease was ruled out with appropriate serologic, imaging, and histologic studies. Specifically, cholestatic diseases such as primary biliary cirrhosis, vanishing bile duct syndrome, ductopenia, primary sclerosing cholangitis, and secondary obstruction of the common bile duct were easily excluded. There was no evidence of exposure to other potentially hepatotoxic compounds such as alcohol, herbal medications, or environmental toxins. Symptoms and laboratory abnormalities appeared less than 2 months after initiation of thioctic acid therapy, disappeared after stopping the medication, and reappeared 1 month after restarting it. This clinical behavior is consistent with a positive rechallenge. Furthermore, clinical and laboratory abnormalities resolved after discontinuation of the drug.

Table 1. Laboratory Values

Days After Drug Initiation	TB (mg/dL)	DB (mg/dL)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	GGT (IU/L)	PT (sec)
Pretreatment	0.35		34	39	109		
30	0.48		55	101	370		12
45	0.99	0.12	114	191	562	592	
47 (admission)	1.54	0.59	43	113	1237		
49 (discontinuation)	1.17	0.51	47	99	1291	648	12.5
52	0.64	0.31	28	65	1283	561	14
54	0.64	0.31	30	57	1110		14.5
60	0.45	0.22	28	57	1052		
75 (discharge)	0.26		29	34	363	250	14
105	0.29		25	29	151	141	12.5
158 (rechallenge)	0.3		25	24	112	88	12
218 (discontinuation)	0.7		100	129	161	180	12
228	0.6		173	280	365	548	12.5
238	0.5		30	64	345	345	12.7
255	0.3		28	28	136	151	
286	0.3		24	26	106	60	12

ALP = alkaline phosphatase (reference range <130 IU/L); ALT = alanine aminotransferase (<35 IU/L); AST = aspartate aminotransferase (<40 IU/L); DB = direct bilirubin (<0.3 mg/dL); GGT = γ-glutamyltransferase (<50 IU/L); PT = prothrombin time (12-14 sec); TB = total bilirubin (<1 mg/dL).

To identify whether there were any other reports of hepatotoxicity from thioctic acid, we performed searches of the medical literature and drug information resources, using the following combinations of words and medical subject heading terms: alpha-lipoic acid, thioctic acid, hepatotoxicity, drug induced liver injury, and liver. We performed a search of MEDLINE (1950-December 5, 2010) and *International Pharmaceutical Abstracts* (1970-December 5, 2010). We also requested a search of databases from the US (Center for Food Safety and Applied Nutrition's Adverse Event Monitoring System and the Food and Drug Administration's MedWatch Adverse Event Reporting System), Europe (European Medicines Agency), and Argentina (National Administration of Medicines, Food and Medical Technology). No reports of hepatotoxicity in humans related to thioctic acid were found in these databases.

Thioctic acid has been proposed as a protective agent against drug-induced liver injury caused by different medications in animal models, and as a treatment for drug-induced liver injury of different causes.[7-11] The potential mechanism of liver toxicity of thioctic acid in this case is largely unknown. There are no reported interactions with other medications, and 600 mg/day is the recommended dose for diabetic polyneuropathy.[1] Our patient's case is the first report of drug-induced liver injury related to thioctic acid, a drug that is widely used since it has been proposed to be a "hepatoprotective" medication. This case reveals the importance of spontaneous postmarketing reporting, even for medications that are considered to be safe.

There is no recommendation about monitoring of liver enzyme levels once thioctic acid is started. In our opinion, monitoring liver enzyme levels during treatment might be logical: every 1-3 months for the first 6 months, and then every 3-6 months. Monitoring liver enzyme levels during thioctic acid treatment may reveal other cases of liver toxicity.

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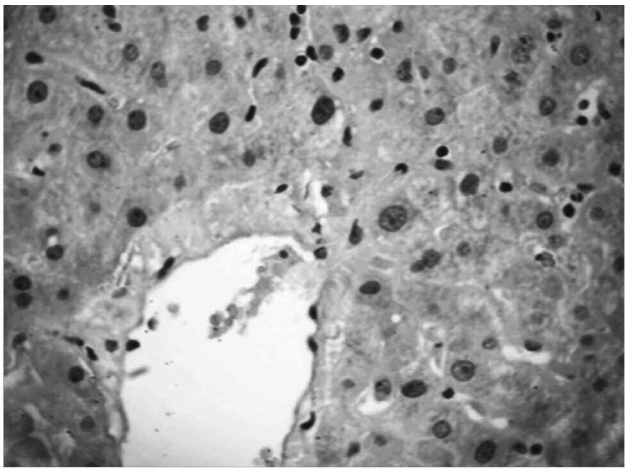

Figure 1. Bland cholestasis. Centrilobular hepatocytes with intracytoplasmic bile pigment. Hematoxylin and eosin; magnification ×400.

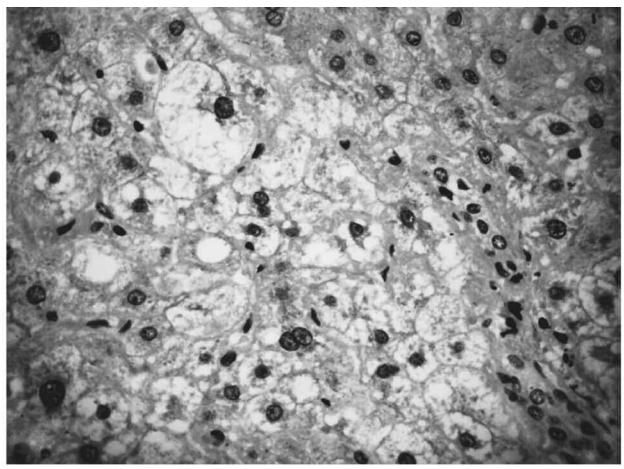

Figure 2. Periportal liver cells are variably enlarged and occasional binucleated hepatocytes are seen. Hematoxylin and eosin; magnification ×400.