CASE REPORT

Drug-induced Liver Injury Caused by Phenprobamate: Strong Probability Due to Repeated Toxicity

Tolga Duzenli[1], Alpaslan Tanoglu[2], Taner Akyol[3], Muammer Kara[4], Yusuf Yazgan[5]

Abstract

Drug-induced liver injury (DILI) is an important cause of morbidity and mortality. DILI can even cause acute liver failure and the need for liver transplantation. Identifying DILI may be particularly difficult because it is actually an exclusion diagnosis and individuals are usually exposed to several drugs during a lifetime. Causality assessment methods are needed for objective diagnosis. The most common methods are; updated Roussel Uclaf causality assessment method (RUCAM), Narenjo adverse drug reaction probability scale and Maria and Victorino (M&V) causality assessment scale. Phenprobamate is a widely used muscle relaxant. Herein we report a rare case of repeated DILI caused by phenprobamate and review the objective diagnostic process for hepatotoxicities. Physicians should be aware of the potential adverse effects of this drug, including hepatotoxicity.

Keywords: Drug-induced liver injury, Phenprobamate, Toxicity.

Euroasian Journal of Hepato-Gastroenterology (2019): 10.5005/jp-journals-10018-1295

Introduction

Drug-induced liver injury (DILI) is an important cause of morbidity and mortality. DILI can even cause acute liver failure and need for liver transplantation. Identifying DILI may be particularly difficult because it is actually an exclusion diagnosis and individuals are usually exposed to several drugs during lifetime.[1-3] Causality assessment methods are needed for objective diagnosis. The most common methods are; updated Roussel Uclaf causality assessment method (RUCAM), Narenjo adverse drug reaction probability scale and Maria and Victorino (M&V) causality assessment scale.[2,3] Phenprobamate is a widely used muscle relaxant in sports medicine.[4] Herein, we report a rare case of repeated DILI caused by phenprobamate. Informed consent is obtained from the patient for the publication of his information and imaging.

Case report

A 28-year-old male patient admitted to our department with complaints of jaundice at the skin, eye, and urine. He had no comorbidities, preexisting liver disease, ethanol or smoking history. He had phenprobamate use for muscle relaxation for 2 weeks and had no other treatment, herbal use or drug addiction. At physical examination, scleras and skin were quite icteric. He had no other pathological findings as rash, fever, arthritis, etc. Neurologic or psychiatric examinations were normal. Laboratory results at admittance are presented in the table by day one (Table 1). The patient had a history of hospitalization one year ago with a similar condition of DILI. At that time, evaluation was made and after the exclusion of all other diseases; the patient was followed-up with the "probable" diagnosis of phenprobamate toxicity. After the withdrawal of phenprobamate, everything about liver got better and fully recovered. But unfortunately, he had begun the same drug again by himself 2 weeks ago for muscle spasms.

We stopped the offending medication and ruled out other potential causes of liver injury by laboratory and radiological screening tests. Viral causes as hepatitis A, B, C, D, E viruses, cytomegalovirus (CMV), ebstein barr virus (EBV), herpes simplex virus (HSV), varicella zoster virus (VZV); biliary obstruction (by ultrasonography); autoimmune etiology by antinuclear antibody (ANA), antismooth-muscle antibody (ASMA), anti-liver kidney microsomal antibody (anti-LKM), antimitochondrial antibody (AMA), immunoglobulin G/G4; genetic diseases as Wilson, Hemochromatosis, α-1 antitrypsin deficiency excluded. Thereafter; we monitored the patient to ensure liver tests normalize. Within one month of withdrawal, laboratory results were significantly normalized.

[1,2,4,5]Department of Gastroenterology, Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey

[3]Department of Gastroenterology, Samsun Gazi State Hospital, Samsun, Turkey

Corresponding Author: Tolga Duzenli, Department of Gastroenterology, Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey, Phone: +90216422020/3502, e-mail: tolgaduzenli@yahoo.com

How to cite this article: Duzenli T, Tanoglu A, *et al*. Drug-induced Liver Injury Caused by Phenprobamate: Strong Probability Due to Repeated Toxicity. Euroasian J Hepatogastroenterol 2019;9(1):49-51.

Source of support: Nil

Conflict of interest: None

Discussion

DILI can develop following the use of many drugs. A high index of suspicion is often necessary to expeditiously establish the diagnosis. It depends on obtaining a careful drug use history and ruling out other potential causes of liver injury.[2,3] There are no specific serum biomarkers or characteristic histologic features that reliably identify a drug as the cause of hepatic injury.[1-3] Causality assessment methods should be used for the correct diagnosis.[2,3] As the most common methods, our patients' score of updated RUCAM were 9 (Table 2), Narenjo adverse drug reaction probability scale was 8 and M&V causality assessment scale were 12, suggesting a likely causal relationship between phenprobamate and toxicity.[4-6]

In the literature, phenprobamate toxicity has revealed itself with neurologic and psychiatric symptoms and treated by hemoperfusion and plasmapheresis.[7,8] In Emet et al. study, their case of phenprobamate overdose (20 tablets of phenprobamate

Table 1: Lab monitorization of the patient (days indicate hospitalization and withdrawal periods)

	ALT (U/L)	*AST (U/L)*	*ALP (U/L)*	*GGT (U/L)*	*D.Bil (mg/dL)*	*T.Bil (mg/dL)*	*Albumin (g/dL)*	*INR*
1-year ago-first hospitalization with "probable" DILI	1256	989	156	256	5.36	7.02	–	–
6 months ago-control	30	25	72	49	0.28	0.97	3.92	1.10
Day 1	4133	1630	146	399	9.06	11.86	4.68	1.12
Day 7	1524	1233	104	116	7.72	11.39	3.74	1.18
Day 14	947	395	85	91	1.83	2.93	3.89	1.07
Day 21	432	128	84	81	1.06	1.82	3.96	1.09
Day 28	122	56	76	56	0.34	1.20	4.12	1.08
Day 180 (outpatient)	28	20	68	51	0.25	0.93	–	–-

DILI, drug induced liver injury; ALT, alanine aminotransferase; AST, aspartat aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; D.Bil, direct bilirubine; T.Bil, total bilirubine; INR, international normalized ratio; U/L, units per litre; mg/dL, milligrams per decilitre; g/dL, grams per decilitre

Table 2: The patients' updated RUCAM for the cholestatic or mixed liver injury of DILI[4]

Items for cholestatic or mixed liver injury	*Score*	*Result*
1. *Time to onset from the beginning of the drug/herb*		
5–90 days (rechallenge: 1–90 days)	+2	+2
<5 or >90 days (rechallenge: >90 days)	+1	
Alternative: Time to onset from cessation of the drug/herb (except for slowly metabolized chemicals: ≤30 days)	+1	
2. *Course of ALP after cessation of the drug/herb*		
Percentage difference between ALP peak and normal		
Decrease ≥50% within 180 days	+2	+2
Decrease < 50% within 180 days	+1	
No information, persistence, increase, or continued drug/herb use	0	
3. *Risk factors*		0
Alcohol use current drinks/d: >2 for women, >3 for men)	+1	
Alcohol use (current drinks/d: ≤2 for women, ≤3 for men)	0	
Pregnancy	+1	
Age ≥ 55 years	+1	
Age < 55 years	0	
4. *Concomitant use of drug(s)/herb(s)*		0
None or no information	0	
Concomitant drug/herb with incompatible time to onset	0	
Concomitant drug/herb with compatible or suggestive time to onset	-1	
Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset	-2	
Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test)	-3	
5. *Search for alternative causes*	Tick if neg.	Tick if not done
Group I (7 causes)		
HAV: Anti-HAV-IgM	-	
HBV: HBsAg, anti-HBc-IgM, HBV-DNA	-	
HCV: Anti-HCV, HCV-RNA	-	
HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	-	
Hepatobiliary sonography/colour Doppler sonography of liver vessels/endosonography/CT/MR	-	
Alcoholism (AST/ ALT ≥ 2)		
Acute recent hypotension history (particularly if underlying heart disease)	-	
Group II (5 causes)	-	
Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases		
Infection suggested by PCR and titer change for	-	
CMV (anti-CMV-IgM, anti-CMV-IgG)		
EBV (anti-EBV-IgM, anti-EBV-IgG)		
HSV (anti-HSV-IgM, anti-HSV-IgG)		
VZV (anti-VZV-IgM, anti-VZV-IgG)	-	
Evaluation of group I and II	-	
All causes—groups I and II—reasonably ruled out	-	
The 7 causes of group I ruled out	-	

Cont...

Cont...

Items for cholestatic or mixed liver injury	*Score*	*Result*
6 or 5 causes of group I ruled out		
Less than 5 causes of group I ruled out	+2	
Alternative cause highly probable	+1	
	0	+2
	–2	
	–3	
6. *Previous hepatotoxicity of the drug/herb*		
Reaction labeled in the product characteristics	+2	
Reaction published but unlabelled	+1	
Reaction unknown	0	0
7. *Response to unintentional reexposure*		
Doubling of ALP with the drug/herb alone, provided ALP below 2N before reexposure	+3	+3
Doubling of ALP with the drugs(s)/herbs(s) already given at the time of the first reaction		
The increase of ALP but less than N in the same conditions as for the first administration	+1	
Other situations		
	-2	
	0	
Total score for the case		9

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; CMV, cytomegalovirus; EBV, Ebstein Barr virus; HSV, Herpes simplex virus; VZV, Varicella Zoster virus; CT, computerised tomography; MR, magnetic resonance imaging; IgM, Immunoglobulin M; IgG, Immunoglobulin G; PCR, polymerase chain reaction; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; N: normal

400 mg, total dose: 8 g) was presented with various muscular and neurological symptoms.[7] The patient had received gastric lavage, activated charcoal, and hemodialysis. After a poor symptomatic recovery, she also had undergone plasmapheresis which revealed complete resolution of symptoms. During her follow-up, she also had transient hyperbilirubinemia and alkaline phosphatase elevation. Tasdemir et al. case was a 16 years old male adolescent presented with drowsiness and confusion which had 37 tablets (14.8 g) of phenprobamate with other drugs.[8] The highest dose was of phenprobamate. By early haemoperfusion and supportive care; the patient had recovered completely.

Our patient had a cumulative toxic dose of phenprobamate rather than acute ingestion and was presented with mixed (cholestatic and liver) type DILI.[9] Serum levels of phenprobamate could not be determined but fortunately, our patient had also recovered by supportive care. In the literature, there is no requirement of transplantation or any methods for prevention for these patients. Also, there is one case report with abuse and dependence of phenprobamate.[10] But our patient is not compatible with this context. In addition to that; Balcı Sengul et al. indicated that phenprobamate was one of the most abused drugs in prisons in Turkey.[11]

In conclusion, although it is generally known that phenprobamate is a safe and effective therapeutic agent for muscle relaxation, physicians should be aware of potential adverse effects of this drug, including hepatotoxicity. Dose reductions or mainly discontinuation of the drug may be needed in such clinical circumstances.

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