Case Report

Propafenone Hepatotoxicity: Report of a New Case and Review of the Literature

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ABSTRACT

Propafenone is a class Ic antiarrhythmic drug. It is a beta-adrenergic blocker that causes bradycardia and bronchospasm. It is metabolized primarily in the liver. Its bioavailability and plasma concentration differ among patients under long-term therapy. They are genetically determined by the hepatic cytochrome P-450 2D6. Hepatic toxicity is highly uncommon. To date, only eight patients were reported in the reviewed world literature. In this article, one new case will be reported emphasizing the importance of medication history taking in patients presenting with new-onset liver enzymes abnormalities.

Key Words: Endoscopic ultrasound, jaundice, liver toxicity, liver biopsies, propafenone

Received: 02.05.2013, Accepted: 18.06.2013

How to cite this article: Younan LB, Barada KA, Faraj WG, Tawil AN, Jabbour MN, Khoury MY, *et al*. Propafenone hepatotoxicity: Report of a new case and review of the literature. Saudi J Gastroenterol 2013;19:235-7.

Propafenone is a class Ic antiarrhythmic drug.[1] It is a beta-adrenergic blocker that causes bradycardia and bronchospasm.[2] It is metabolized primarily in the liver.[3,4] Its bioavailability and plasma concentration differ among patients under long-term therapy. They are genetically determined by the hepatic cytochrome P-450 2D6.[5]

Hepatic toxicity is highly uncommon.[6] To date, only eight patients were reported in the reviewed world literature.

In this article, one new case is reported emphasizing the importance of medication history taking in patients presenting with new-onset liver enzymes abnormalities.

CASE REPORT

A 67-year-old female patient presented to the emergency department of the American University of Beirut Medical Center because of the progressive appearance of painless jaundice of two weeks duration.

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DOI: 10.4103/1319-3767.118137

The patient's past medical history was noted for left breast cancer (in remission). She denied alcohol intake or illicit drug abuse.

Six weeks prior to the onset of jaundice, she had presented with high-rate atrial fibrillation and was commenced on propafenone at 300 mg/day.

Upon presentation, she was icteric. The physical examination revealed minimal nontender hepatomegaly.

A computed tomography scan performed at another facility showed prominent common bile and pancreatic ducts suggesting a double duct sign. Her initial serum bilirubin was 9.4/7.7 mg/dL, alkaline phosphatase of 384 IU/L. Her alanine transferase was 213 IU/L and aspartate transferase 228 IU/L. Her CA19-9 was 70 IU/mL [Table 1]. Endoscopic ultrasound done at our center showed normal common bile and pancreatic ducts and no ampullary or pancreatic masses. Subsequently, viral serologic markers (IgM hepatitis A virus, IgM Hepatitis B core, Hepatitis C virus antibodies, Epstein-Barr virus, Cytomegalovirus) were negative. The anti-nuclear, anti-smooth muscle, anti-mitochondrial, and anti-liver and anti-kidney microsome antibodies' levels were within normal limits. A Magnetic resonance cholangiopancreatography

suggested a left hepatic stricture, but Endoscopic retrograde cholangiopancreatography was normal.

A liver biopsy via a trucut needle showed active portal and periportal inflammation with moderate macrovesicular steatosis, and bile ductular proliferation [Figure 1a and b].

Withdrawal of propafenone was associated with gradual decrease in serum alkaline phosphatase and gamma-glutamyl transferase along with normalization of the aminotransferase levels and CA19-9.

DISCUSSION

A diagnosis of acute propafenone toxicity was made on the basis of the following observations:

1. A temporal relationship between the intake of the drug and the development of symptoms[5,6]
2. Clinical and biochemical recovery occurred following the withdrawal of the drug[6]
3. Exclusion of other causes of liver dysfunction[7] and
4. The histologic changes were consistent with drug toxicity.[8]

We performed a Naranjo evaluation[9] to determine the probability that the clinical event experienced by the patient was due to propafenone administration. Naranjo algorithm is a questionnaire for determining the likelihood of whether an adverse drug reaction is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite (>9 points), probable (between 5 and 8 points), possible (between 1 and 4 points), or zero as

Table 1: Initial and follow-up laboratory data

Patient	Laboratory data	
	At initial presentation	Six weeks after medication withdrawal
Jaundice	+	–
Pruritus	+/–	
Abdominal pain	–	
WBC (count/mm^3)	8300	8000
Platelet count (mm^3)	260	290
Bilirubin T/D (mg/dL)	9.4/7.7	1/0.5
AP/GGT (IU/L)	384/1024	156/311
ALT/AST (IU/L)	213/228	60/61
LDH (IU/L)	220	100
TSP/Albumin (g/L)	4/3.6	4/3.8

AP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, ALT: Alanine transferase, AST: Aspartate transferase, LDH: Lactate dehydrogenase, TSP: Total serum proteins, WBC: White blood cell

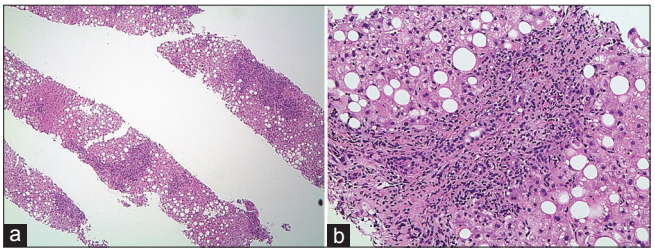

Figure 1: (a) Liver biopsy revealed portal and periportal inflammatory infiltrate. The liver parenchyma exhibited macrovesicular steatosis (magnification ×40). (b) Prominent bile duct injury with associated bile ductular proliferation. The mixed inflammatory infiltrate consists of eosinophils, neutrophils, lymphocytes, and plasma cells (magnification ×200). Mild periportal hepatocyte feathery degeneration is noted. There is no evidence of fibrosis

Table 2: Clinical, biochemical, and histopathology findings in patients with propafenone hepatotoxicity as reported in the world's literature

Patient	Author	Sex/age (yr)	Latency (wk)	Symptoms	ALT/AP	Biopsy
1	Schuff-Werner[1]	F/35	2	Jaundice	289/826	Ballooning of hepatocytes, portal tracts enlargement, bile duct proliferation
2	Schuff-Werner[1]	F/60	4	Vomiting	115/ND	Not available
3	Konz[3]	M/84	ND	Jaundice	75/540	Portal tracts enlargement with granulocytes, lymphocytes and macrophages infiltrates, round cell infiltration of bile ducts
4	Mondardini[7]	M/66	2	Pruritus, jaundice and abdominal pain	127/553	Portal tracts enlargement with granulocytes infiltrates and bile duct proliferation
5	Elizalde[8]	M/62	3	Jaundice	501/1512	Not performed
6	Cocozzella[10]	F/67	6	Pruritus, jaundice, abdominal pain	22/770	Not performed
7	Spinler[6]	F/71	4	Not available	N/A	Not performed
8	Cocozzella[10]	F/69	28	Pruritus, jaundice, abdominal pain, asthenia	100/1020	Portal tracts enlargement with lymphocytes, monocytes and macrophages, bile duct proliferation and ballooning of hepatocytes, cholestasis
Our case		F/67	6	Jaundice	213/384	Portal and periportal inflammatory infiltrates/ macrovesicular steatosis and bile duct

M: Male, F: Female, N/A: Not available, ND: Not documented, ALT: Alanine transferase, AP: Alkaline phosphatase

doubtful. We obtained a score of 7, indicating a probable adverse drug reaction from propafenone use.

This report is the eighth in the world's literature describing hepatotoxicity related to propafenone [Table 2]. The clinical presentation of propafenone hepatotoxicity can be cholestatic and/or hepatocellular.[6,7] It presents with jaundice as reported in all cases. The latency period varied between two and six weeks. Only one reported case presented after 28 weeks [Table 2]. No cases of fulminant liver failure related to propafenone have been reported.

Our experience suggests that early recognition of liver toxicity and early drug withdrawal can lead to complete resolution of symptoms. Obtaining a detailed history about recent medication change is paramount in evaluating patients with new-onset jaundice.

In conclusion, although this drug-induced liver injury is rare, it should not be overlooked in patients complaining of an acute cholestatic syndrome and jaundice of obscure origin.

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Source of Support: Nil, **Conflict of Interest:** None declared.

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