Propafenone-related cholestatic hepatitis in an elderly patient

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Hepatic toxicity caused by propafenone is extremely rare. We here describe a case of acute cholestasis secondary to propafenone treatment in an elderly male with no history of preexistent liver disease. The clinical picture and time course of the symptoms seem to be compatible with a direct toxic reaction. Age-related delays in hepatic drug metabolism should explain the hazardous increase in the bioavailability of this drug. Despite the rarity of this complication, propafenone should be considered as a potential cause of drug-induced cholestasis in elderly patients. The literature on the hepatotoxicity of propafenone is also reviewed.

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Introduction

Propafenone is a class 1C antiarrhythmic drug used for the control of ventricular and supraventricular arrhythmias; it is also effective for the cardioversion of atrial fibrillation[1]. It prolongs the duration of both the PR and QRS intervals and also has negative inotropic and beta-blocking effects[1].

Propafenone is generally well tolerated, but it can cause both cardiovascular and non-cardiovascular side effects. The former include rhythm changes with bundle branch block or symptomatic bradycardia. Reactions of the nervous and gastrointestinal (nausea, constipation, dysgeusia) systems have also been reported[2]. In a meta-analysis of the effects of propafenone, the overall mortality was extremely low at 0.3%, but older age and prior myocardial infarction were associated with an increased risk of adverse events[2]. Cases of hepatic toxicity caused by this drug are extremely rare (0.1-0.2%); clinical manifestations include acute cholestasis or signs of liver-cell necrosis[3].

We report a case of propafenone-related acute cholestasis in an elderly male with no history of pre-existent liver disease.

Case report

In July 2001, an 84-year-old male presenting with pruritis, scleral jaundice, dark urine and acholic feces but no hepatomegaly was referred to our Institute for evaluation. The patient had been on anti-hypertensive beta-blocker therapy for 4 years. In June 2001, following the onset of a hyperkinetic supraventricular arrhythmia, propafenone (450 mg/day orally) was prescribed. The patient presented with the symptoms cited above after 3 weeks of therapy with the antiarrhythmic drug. Ethanol abuse and/or the use of toxic substances were excluded on the basis of the patient's medical history, reports of family members, and the results of DSM IV evaluation[4].

The hepatic ultrasound examination showed no signs of fatty liver or dilation of the bile or Wirsung ducts. Laboratory analysis at the time of admission revealed: normal complete blood count; alanine transaminase 116 IU/l (normal values < 45 IU/l); aspartate transaminase 215 IU/l (normal values < 45 IU/l); γGT 942 IU/l (normal values < 5I IU/l); alkaline phosphatase 1655 IU/l (normal values < 190 IU/l); total bilirubin 10.7 mg/dl; direct bilirubin 9.5 mg/dl; lactic dehydrogenase, serum albumin and prothrombin time were within normal limits. Serology was negative for past or present HAV, HBV, HCV, HEV or cytomegalovirus infections. The serum levels of carcinoembryogenic antigen, alpha-fetoprotein, and carbohydrate antigen 19-9 were all within normal limits. Urinalysis confirmed the presence of bilirubin and urobilinogen. The ECG showed no conduction abnormalities (i.e. QRS prolongation or conduction block) attributable to an excessive dosage of propafenone. On magnetic resonance cholangiography, the hepatic parenchyma

presented uniform signal intensity with no evidence of focal lesions or perfusion defects; the course and caliber of the intra and extrahepatic bile ducts were normal and there were no filling defects. The gall bladder was normally distended with no parietal alterations; numerous intraluminal stones were noted. The findings were compatible with the criteria for drug-induced hepatitis by Benichou[5] and Maria and Victorino[6].

Propafenone was discontinued and intravenous fluid replacement was started. After 1 week, the patient's symptoms had improved considerably and repeat blood analysis showed: aspartate transaminase 75 IU/l; alanine transaminase 159 IU/l; alkaline phosphatase 1433 IU/l; γGT 741 IU/l; direct bilirubin 5.1 mg/dl.

The ECG, echocardiogram and 24-hour Holter monitoring results showed no evidence of arrhythmia. The patient was discharged in good clinical conditions after 2 weeks with instructions to continue the beta-blocker therapy; a cycle of ursodesoxycholic acid (300 mg bid) was also prescribed. One month later the transaminase, γGT and bilirubin levels had returned to normal (Figs. 1 and 2), and cardiac evaluation revealed no anomalies or conduction defects. At the 6-month follow-up visit, the patient was asymptomatic and on beta-blocker therapy alone. Holter monitoring did not reveal any rhythm disturbances.

Discussion

The cholestatic syndrome is a common feature of drug-induced hepatic damage. It has been estimated that 2-5% of all hospital admissions for jaundice and 10% of those for acute hepatitis can be attributed to drug toxicity, and these figures are even higher in the over-50 age group[7,8]. Upon withdrawal of the culprit drug, symptoms may resolve spontaneously. These cases are associated with a favorable prognosis. In other cases, the disease persists for 6 months or longer, evolving towards a drug-induced cholangiopathy with variable manifestations of ductopenia, including biliary cirrhosis[9]. Drug-related cholestasis has been reported for estrogens, ciprofloxacin, ticlopidine, captopril (irbesartan), the statins, risperidone, metformin and recently the cyclooxygenase-2 inhibitors[10,11].

The mechanisms underlying drug-induced cholestasis can lead to alterations in bile-acid uptake (which is mediated by Na^+-dependent and independent carriers), intracellular transport, canalicular secretion [(an active process mediated by P-glycoproteins of the ABC (ATP-binding cassette)] families, and/or multidrug resistance[12].

The mechanism underlying propafenone-induced cholestasis is still unclear. The processes of hepatic biotransformation leads to the formation of metabolites that can act as electrophilic reagents or free radicals. These molecules may cause hepatic damage in various ways, e.g. depletion of reduced glutathione, interaction with various proteins, lipids and/or nucleic acids or stimulation of lipid peroxidation. Their covalent binding to and/or alteration of hepatic proteins, including cytochrome P450, can also create the prerequisites for a process of sensitization and immune-mediated injury, with results that range from liver-cell necrosis and apoptosis to hypersensitivity to cytokines and inflammatory mediators[11,13].

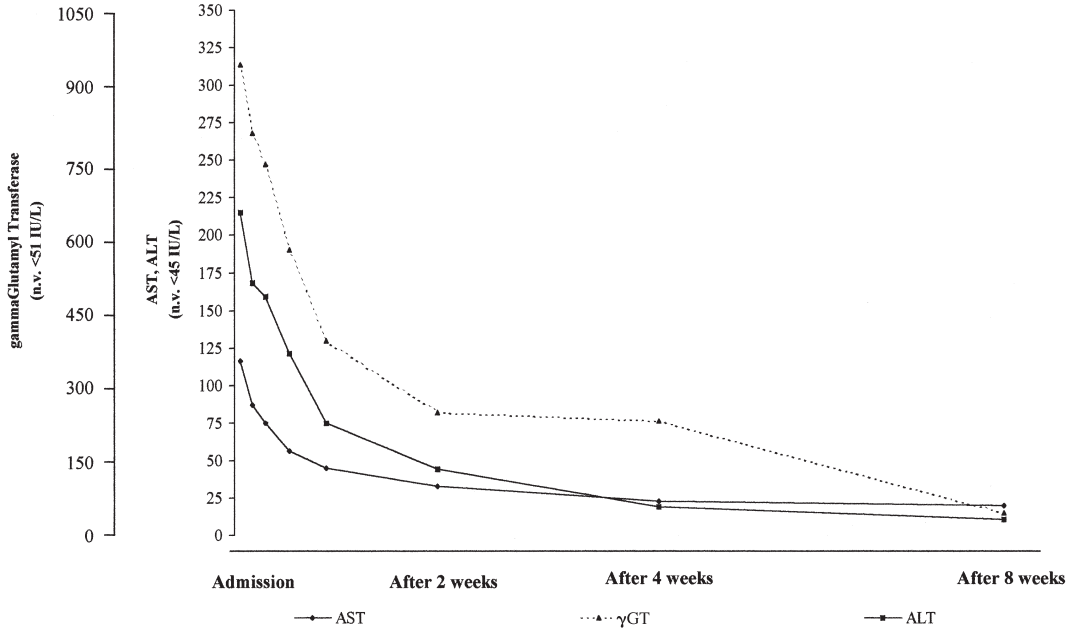

Figure 1. *Serum transaminase and γ-glutamyl transpeptidase (γGT) levels. Two weeks after the discontinuation of propafenone, jaundice subsided and the serum levels of liver enzymes returned to a near-normal range. ALT = alanine transaminase; AST = aspartate transaminase.*

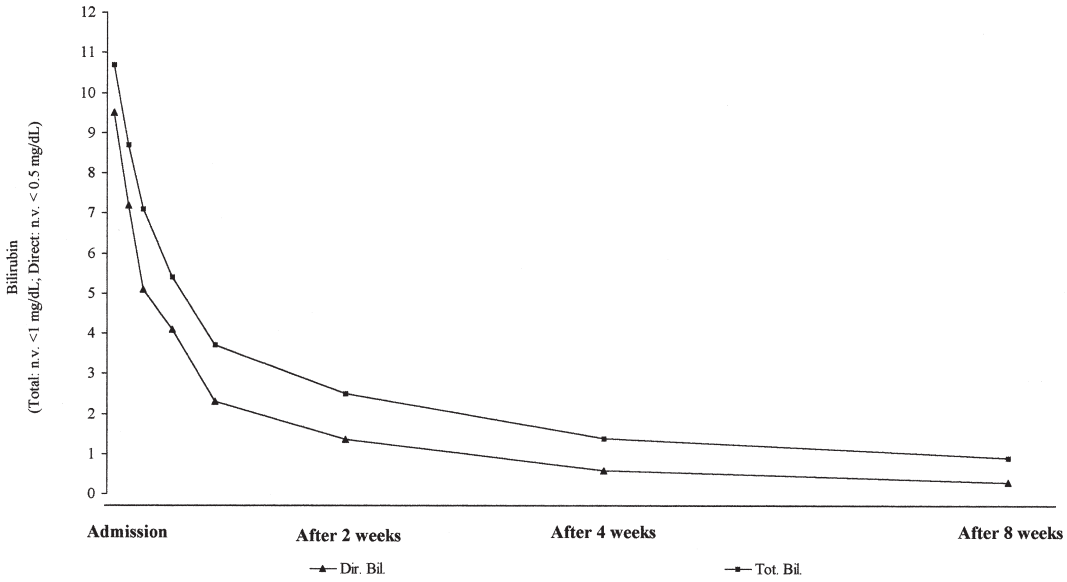

Figure 2. *Significant decrease in the total and direct bilirubin levels after discontinuation of propafenone.*

In the case described here, the diagnosis of drug-induced cholestatic hepatitis was based on the serological indices of cell necrosis and cholestasis. In view of the patient's advanced age and the prompt response to suspension of the suspected culprit drug, liver biopsy was deferred. The clinical classification of drug-induced hepatotoxicity published by the US Public Health Service in 1979 distinguishes two types of reactions: type I, which are predictable and both dose- and time-dependent, and type II, which are unpredictable, dose- and time-independent[14]. Many authors, however, prefer to substitute these terms with "direct" and "indirect" toxicity, respectively.

In the present case report, the clinical picture and time course of symptoms seem to be compatible with a type II, or indirect toxic reaction. In fact, the patient's symptoms first appeared 2 weeks after he had been started on the antiarrhythmic. The early onset of symptoms (within a few days) is evidence for a type I reaction, while unpredictable reactions show a different and variable latency between the initiation of drug assumption and the onset of symptoms and clinical findings of liver disease. In particular, an intermediate (1-8 weeks), observed in our patient, or a long latency (> 12 months) is a typical feature of the indirect toxic reaction[15].

The hepatic metabolism of drugs is complex, and can be influenced by the simultaneous use of other drugs as well as by other endogenous and exogenous substances which can cause induction or inhibition of the enzymatic pathways. It can also be affected by smoking and alcoholic beverages, the subject's nutritional status, dietary components (e.g., fruit juices, contaminants) and concomitant diseases[11]. All these conditions were absent in our patient. On the basis of the morphological and functional liver studies that were performed, we can exclude the coexistence of viral or alcohol-related liver disease, which can alter the bioavailability of propafenone. In subjects with cirrhosis, for example, an increased bioavailability together with a delayed clearance and increased levels of the free fraction of propafenone have been documented after a single intravenous administration of the drug[16].

Orally administered propafenone is characterized by a low bioavailability, which varies from 5 to 30% and is related to the first-pass hepatic metabolism and to the drug's high rate of carrier protein binding (95%)[1]. Propafenone is predominantly metabolized by hepatic CYP2D6. The genetic polymorphism of this enzyme has important implications, and both slow and rapid metabolizers have been identified[17-20]. Typical propafenone-related toxic reactions include neuropathy, and central nervous system effects.

In our case the absence of neurological signs and of ECG changes (i.e. QRS prolongation and/or conduction block) suggests a mechanism other than a reaction due to an excessive dosage of propafenone.

In conclusion, this case illustrates the need for close monitoring for possible hepatic toxicity in elderly subjects taking propafenone since, even in the absence of pre-existent liver disease, the risk of an indirect toxic effect is unpredictable.

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