Cholestatic hepatitis due to propafenone in father and daughter

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To the Editor,

Propafenone, which is primarily metabolized in the liver by cytochrome p-450 2D6, is a classic IC anti-arrhythmic drug used for ventricular and supraventricular arrhythmias. Literature on how it induces hepatotoxicity is extremely rare, and the underlying mechanism remains unknown. However, a propafenone metabolite-induced hypersensitivity or idiosyncratic toxic reaction is implicated (1).

A 65-year-old man with itching, weakness, and nausea, and who 10 years earlier was operated for a pituitary tumor, and since then had been on 100 mcg of levothyroxine and 5 mg of prednisolone, was found to have elevated liver enzyme levels. He consulted the gastroenterology department. He had no alcohol consumption history, and had been started on propafenone (300 mg/day) for rapid atrial fibrillation insufficient for beta blocker therapy 45 days earlier. Physical examination revealed dermal scratch marks but no signs of liver disease. His laboratory test results were as follows: total bilirubin,1.96 mg/dl, direct bilirubin,0.69 mg/dl, AST,182 IU/L, ALT,306 IU/L, ALP,323 IU/L, GGT,1198 IU/L; and negative viral serology (IgM anti-HAV, IgM anti-HBc, HBs Ag, and anti–HCV) and autoimmune antibodies (ANA, anti-LKM-1, AMA, and SMA). A hemogram revealed his eosinophil percentage to be 4.98%, and an abdominal ultrasonogram excluded biliary obstruction. 1 week after propafenone cessation, his symptoms vanished and his enzyme levels regressed. The consulting cardiologist prescribed smoking cessation, avoidance of caffeine, propafenone cessation, and bisoprolol 100 mg/day.Ten months after the presentation, without notifying his physician, he took propafenone (300 mg/day) for severe palpitation. Similar symptoms and laboratory findings were observed 1 week later, and he was instructed to discontinue propafenone use. Ten days after propafenone cessation, his liver enzyme levels returned to normal.

A year later, his 41-year-old daughter reported frequent bigeminy of ventricular premature beats, which was unresponsive to beta blocker therapy and amiodarone. She was started on propafenone (300 mg/day). Given that she had a paternal hepatotoxicity history, she presented to the gastroenterology clinic, but her examination and tests were negative for all liver disorders. Her liver enzymes were monitored weekly during her propafenone treatment, and on week 3, she began having itches coupled with elevated ALT (17 IU/L to 84 IU/L) and GGT (30 IU/L to 105 IU/L) levels. Upon propafenone cessation, her itching vanished and her liver enzyme levels returned to normal.

The development of cholestasis-related clinical and biochemical abnormalities after drug intake, and regression of signs and symptoms after drug cessation, suggest drug-induced hepatotoxicity. The absence of liver disease and recurrent clinical picture after propafenone re-institution supports the diagnosis. Additionally, a first degree relationship between ~~our~~ the patients suggests a genetic predisposition(1,2).

As in these cases, a latent period of 2-6 weeks is observed after drug intake. Also, in line with existing literature, peripheral blood eosinophilia was noted as a supportive sign for idiosyncratic allergic reactions in the first case (1,3,4).

Propafenone-induced hepatotoxicity is rare and no fatal case has been reported (2). However, liver enzymes should be monitored when patients on propafenone complain of symptoms and signs like itching, jaundice, abdominal pain, and nausea.

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