Flecainide and elevated liver enzymes in α1-antitrypsin deficiency

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Introduction

Flecainide is a commonly used drug for rhythm control in atrial fibrillation (AF) with a good safety profile1,2 when used in the absence of structural heart disease. Flecainide has been associated with acute hepatitis and cholestasis.3-6 Owing to the small number of reported cases, however, the nature of this purported association and potential predisposing factors have not been clearly established. However, in view of the growing number of individuals with AF in the North American population (~2–4 million),7 who may require long-term medical treatment or treatment prior to ablation therapy,2 it is important to identify predisposing conditions for adverse liver reactions associated with flecainide.

We therefore report the case of a 72-year-old man of Northern European ancestry with α1-antitrypsin deficiency. This condition is rare, with 1 in 2500 individuals carrying the gene in those of the Northern and Western European ancestry. It is a genetic disorder that results in production of an abnormal antitrypsin that lacks antitrypsin activity that would normally protect the lungs from neutrophil elastase. The abnormal α1-antitrypsin accumulates in liver cells and may lead to cirrhosis. Lungs and liver are therefore rendered more susceptible to damage by toxins, especially lung damage in smokers, resulting in emphysema and chronic obstructive pulmonary disease.8 Our patient developed a clinically significant rise in liver enzymes and abdominal discomfort in response to flecainide prescribed for rhythm control to abort increasingly frequent paroxysmal attacks of AF.

Case report

The patient (DJAJ) was a 72-year-old white man with a 6-year history of recurrent episodes of paroxysmal AF that occurred at monthly intervals and had been documented by 24-hour Holter monitor with symptom–arrhythmia correlation. He had no history or symptoms of coronary arterial disease or hypertension, although he had an apoE 4 genotype9 with a raised serum cholesterol, for which he had been prescribed lovastatin (20 mg) several years previously. The patient discontinued the statin after a few days owing to right upper quadrant “heaviness.” No transaminase levels were measured. Statin therapy was not restarted. More recently the patient had carotid and large coronary vessel magnetic resonance imaging. No evidence of atheroma or arteriosclerosis was detected. He also had obstructive pulmonary disease.8 Our patient developed a 6-year history of recurrent episodes of paroxysmal AF that had become symptomatic and was impairing his quality of life.

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Because of this increasing frequency of symptomatic AF, the patient consulted his cardiologist. His cardiac function overall was assessed as normal for his age following thoracic echocardiography that also demonstrated a trace of mitral, tricuspid, and pulmonic valve regurgitation. Left ventricular proximal septal thickening; and discrete nodular thickening of the noncoronary cusp of a trileaflet aortic valve. He was prescribed metoprolol 25 mg twice a day and flecainide 50 mg twice a day. During the next 5 days, he experienced only one 8-hour episode of AF on day 2 of flecainide and was able to swim, walk briskly, and climb stairs, as previously. However, on day 2 of flecainide he became conscious of right upper quadrant (RUQ) discomfort, which was brought on by walking. By the fourth day, walking resulted in considerable RUQ pain with each step and there was also discomfort over the same area, even when swimming. Flecainide was discontinued on the fifth day. At this time ultrasound detected no liver abnormality apart from a number of hemangiomas that had previously been documented. At the end of 5 days of flecainide administration, both transaminases (alanine transaminase and aspartate transaminase) and alkaline phosphatase levels were elevated, similar to other reports of adverse liver reactions associated with flecainide (Figure 1A, B). A comprehensive liver evaluation was undertaken at this point, which ruled out underlying infectious (hepatitis A, B, and C), autoimmune, or metabolic (hemochromatosis, Wilson disease) liver disease. However, α1-antitrypsin deficiency was identified (mean = 0.77 g/L; range, 0.63–0.85 g/L on multiple measurements, lower-normal limit 0.89 g/L). During this period, synthetic liver function (prothrombin time, bilirubin, and albumin) remained normal. On discontinuation of flecainide, the fall in transaminases was rapid, and within 3 days of discontinuation of flecainide all discomfort abated. After 1 day, AF returned with increasing frequency and with some episodes lasting 12–36 hours (Figure 1C). A lower dose of flecainide (12.5–100 mg/d; average 52.5 mg/d) was reintroduced for 2 weeks (Figure 1D). However, because of recurrent RUQ pain on walking, flecainide was again discontinued after 14 days. The RUQ pain during the low-dose flecainide administration was less severe and sporadic than the predictable exercise-induced severe pain experienced after higher-dose flecainide administration. The rechallenge with lower-dose flecainide also resulted in significantly less of a transaminase rise (Figure 1A, B), and bilirubin levels fluctuated throughout but showed no obvious relation to flecainide administration. Flecainide was subsequently discontinued and a trial of disopyramide 200 mg/d was undertaken (Figure 1D). Although there was some apparent reduction in length of daily AF episodes (Figure 1C), it was discontinued owing to urinary symptoms consisting of hesitancy and poor stream. Prostate-specific antigen rose from a baseline of 1.6 ng/L to 2.0 ng/L and back to baseline 5 days after disopyramide withdrawal. There was no change in liver enzymes during disopyramide administration.

Conclusion

The current case adds to the growing body of reports that flecainide may cause abnormal liver enzymes. However, adverse liver reactions associated with flecainide remain rare, with only a few reported cases in the literature. As a result, liver enzymes are not routinely monitored; and severe RUQ discomfort was required to trigger investigation of liver enzymes in our case.

In our case, the patient had α1-antitrypsin deficiency, a rare condition for which 1 in 2500 individuals carry the gene among those of Northern and Western European ancestry, which might have contributed to the observed elevated liver enzymes. Flecainide-mediated hepatocellular changes may induce cytokine release and stimulate the synthesis of α1-antitrypsin, an acute-phase protein. However, in patients with α1-antitrypsin deficiency, the protective effect of α1-antitrypsin may be reversed and enhance hepatocellular damage, since a misfolded and therefore potentially toxic serpin α1-antitrypsin is produced. The major clearance route of flecainide is via the hepatic cytochrome p450 system...
is the cause of the marked rise in transaminases. However, the presence of Gilbert syndrome may also have been a contributing factor in this case, although the relatively high frequency of Gilbert syndrome, 3%–12% of the population, does not suggest that it alone would account for the marked rise in transaminases with alkaline phosphatase, atrial fibrillation occurrence, and drug use in a 72-year-old man.

**Figure 1**

Time course of drug exposure and effect on liver transaminase and alkaline phosphatase.
We conclude that when flecainide treatment is initiated, RUQ discomfort, as in our patient, should trigger discontinuation of the drug and measurement of serum α1-antitrypsin levels in addition to serum transaminases.

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