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 profile[1,2] 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 genotype[9] 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 Gilbert syndrome. The patient was a vegan, was a nonsmoker, consumed < 1 drink of alcohol/week, and had taken regular vigorous exercise throughout his life. Recently AF had become symptomatic and was impairing his quality of life.

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KEY TEACHING POINTS

- Flecainide is a first-line drug for rhythm control with a long history of clinical use and, when given in conjunction with a β-blocker, is associated with remarkably few side effects.
- α1-Antitrypsin is produced in the liver and protects pulmonary tissue from neutrophil elastase. Genetically determined α1-antitrypsin deficiency in its severe form results in lung damage, emphysema, and chronic obstructive pulmonary disease and the accumulation of misfolded α1-antitrypsin protein in the liver, which is associated with development of cirrhosis.
- This study of a patient with α1-antitrypsin deficiency who, on repeated flecainide challenge for control of atrial fibrillation, showed marked rises in serum transaminases with right upper quadrant pain indicates that α1-antitrypsin deficiency may increase susceptibility to the adverse hepatic effects of flecainide.
- Patients with right upper quandrant pain on flecainide should have the drug stopped and trasaminases and α1-antitrypsin measured.
- If α1-antitrypsin deficiency exists, then drugs without hepatic metabolism should be preferred; and if drugs with hepatic metabolism are used they should be closely monitored.
- It is also possible that Gilbert syndrome may have contributed to the hepatic effects seen with flecainide.

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 transthoracic echocardiography that also demonstrated a trace of regurgitation at mitral, tricuspid, and pulmonic valves; 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 1 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).[3–6] 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.[3–6] 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,[8] 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.[8] 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

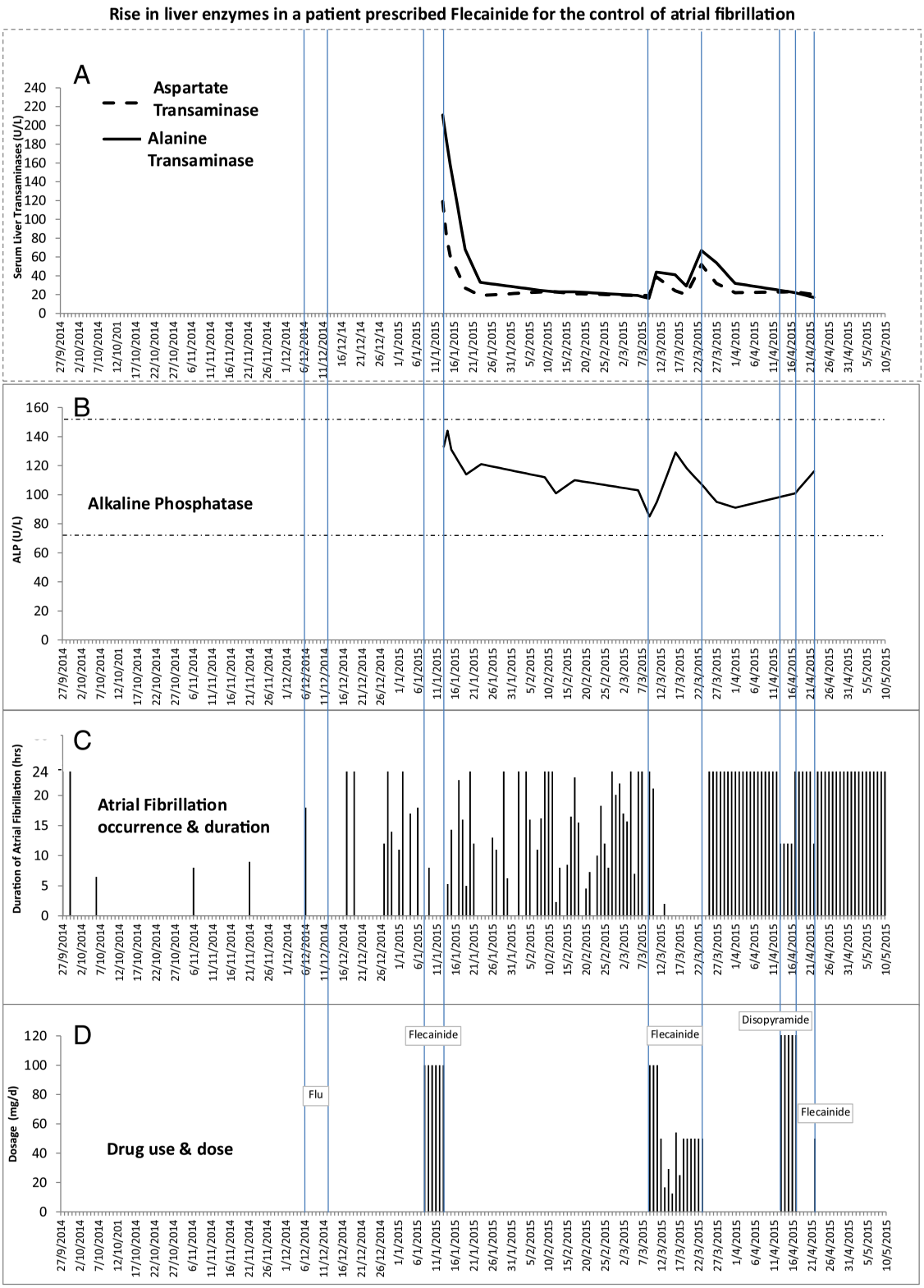

Figure 1 Time course of atrial fibrillation/flutter and the effect of flecainide administration on serum transaminases with alkaline phosphatase, atrial fibrillation occurrence, and drug use in a 72-year-old man.

and urinary excretion, with approximately 30% excreted unchanged. However, the 2 main metabolites of the drug, 1 of which retains some activity, are both conjugated prior to urinary excretion. The presence of Gilbert syndrome may therefore also have been a contributing factor in this case, although the relatively high frequency of Gilbert syndrome, at 3%–12% of the population, does not suggest that it alone is the cause of the marked rise in transaminases.

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.

References

1. Aliot E, Capucci A, Crijns HJ, Goette A, Tamargo J. Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation. Europace 2011;13(2):161–173.
2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130(23):e199–267.
3. Kuhlkamp V, Haasis R, Seipel L. [Flecainide-induced hepatitis]. Z Kardiol 1988;77(10):678–680.
4. Mikloweit P, Bienmuller H. [Drug-induced intrahepatic cholestasis caused by flecainide acetate and enalapril]. Internist (Berl) 1987;28(3):193–195.
5. Tamargo J, Capucci A, Mabo P. Safety of flecainide. Drug Saf 2012;35(4): 273–289.
6. Hopmann G, Surmann T. [Cholestatic jaundice during flecainide therapy]. Dtsch Med Wochenschr 1984;109(48):1863.
7. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. J Am Heart Assoc 2015;4(1):e001486.
8. Fregonese L, Stolk J. Hereditary alpha-1-antitrypsin deficiency and its clinical consequences. Orphanet J Rare Dis 2008;3:16.
9. Kang AK, Jenkins DJ, Wolever TM, et al. Apolipoprotein E R112; R251G: a carboxy-terminal variant found in patients with hyperlipidemia and coronary heart disease. Mutat Res 1997;382(1-2):57–65.