A rare case of flecainide-induced encephalopathy

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Introduction

Antiarrhythmic drugs such as flecainide are cornerstones of treatment for cardiac arrhythmias including atrial fibrillation. Although there are many benefits to antiarrhythmic drug therapy, there are also significant side effects. These side effects can be exacerbated by drug-drug interactions that affect the metabolism of antiarrhythmic drugs. Here, we report a rare case of flecainide-induced encephalopathy in a patient who was concomitantly taking the selective serotonin reuptake inhibitor fluoxetine and the class IC antiarrhythmic flecainide.

Case report

A 71-year-old woman with atrial fibrillation, multifocal atrial tachycardia, and mood disorder was initially admitted with syncope. The cardiac work-up showed a structurally normal heart and no significant coronary artery disease but substantial atrial arrhythmias, including atrial fibrillation and multifocal atrial tachycardia complicated by frequent episodes of rapid ventricular rates. A trial of sotalol failed owing to QTc prolongation, which was likely exacerbated by her multiple psychiatric medications, including fluoxetine 60 mg daily, which was a chronic medication for the patient. She was therefore initiated on flecainide 100 mg twice a day and metoprolol, which improved her heart rate and allowed for her to be discharged. She was readmitted 3 days later with tachycardia and altered mental status. At that time, she was noted to have agitation, confusion, and visual hallucinations. She was not oriented to person, place, or time and required restraints owing to the extent of her agitation. The work-up for her encephalopathy was initially unrevealing; her potassium was 3.3 and magnesium was 1.6, her hepatic function was normal (AST 12, ALT 11, alkaline phosphatase 87), and her creatinine clearance was 52.5 mL/min. An infectious work-up was negative, and electroencephalogram did not show seizure activity. Psychiatry was ultimately consulted and suspected the encephalopathy was secondary to drug effect.

KEYWORDS Antiarrhythmic drugs; Flecainide; Encephalopathy; Drug-drug interaction; Cytochrome P450

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KEY TEACHING POINTS

- Flecainide is metabolized by the CYP2D6 isozyme. It is important to recognize that medications that affect the cytochrome P450 system may alter flecainide metabolism.
- Given the prevalence of psychiatric mediations, providers must be aware of drug-drug interactions of psychiatric mediations with antiarrhythmics.
- Encephalopathy is a rare but serious side effect of flecainide. Encephalopathy can resolve with cessation of flecainide therapy.

Confusion and hallucinations are rare symptoms of flecainide toxicity, but given the recent addition of this medication, there was concern that this drug was the culprit for her encephalopathy. This hypothesis was additionally supported by the fact that the patient was concomitantly taking fluoxetine, which is a potent cytochrome P450 CYP2D6 inhibitor[1] and can therefore lead to increased levels of flecainide, which is metabolized by the CYP2D6 isozyme. Additionally, flecainide metabolism worsens with age, especially after 70 years of age,[2] and with reduced creatinine clearance, since flecainide is also excreted in the urine.[3] Fluoxetine was held for 3 days and then flecainide was discontinued. A flecainide serum level was obtained 8 hours after the last dose of flecainide and was 538 ng/mL (reference range 200–1000 ng/mL). After fluoxetine, a known inhibitor of flecainide metabolism, was held and flecainide was discontinued, the patient's encephalopathy resolved and her mental status remained stable, even after fluoxetine was reintroduced 4 days later. Given the patient's difficult-to-control atrial arrhythmias and intolerance of multiple antiarrhythmic therapies (especially in conjunction with essential psychiatric medications), the patient ultimately underwent an atrioventricular nodal ablation and dual-chamber pacemaker implantation.

Discussion

This case demonstrates that encephalopathy is a rare but serious side effect of the class IC antiarrhythmic flecainide, although the mechanism of this side effect is not well

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understood. Flecainide has a narrow therapeutic range and narrow window of safety, which increases the risk of side effects from this medication.[4] Rare cases of neurotoxicity owing to flecainide have previously been reported.[5–8] Our case importantly highlights a drug-drug interaction between flecainide and a selective serotonin reuptake inhibitor, fluoxetine. This interaction affects the metabolism of the class IC antiarrhythmic and likely led to the rare side effect of encephalopathy in our patient. When fluoxetine was held, the metabolism of flecainide was no longer inhibited. This, combined with discontinuing flecainide, led to resolution of the patient's encephalopathy. Additionally, other etiologies of encephalopathy were ruled out, leaving flecainide as the likely culprit.

Although rhythm disturbances such as atrial fibrillation affect a significant patient population and require pharmacotherapy, there are also many psychiatric disorders that require medications for management. There are known cardiovascular considerations in antidepressant therapy such as QTc prolongation[9]; however, other effects, such as metabolism interactions, should also be understood by prescribers. As highlighted in this case, psychiatric medications and antiarrhythmics may have significant drug-drug interactions. The benefits of antiarrhythmic drugs must always be weighed against the risks of side effects. Therefore, it is essential to understand the mechanism of action and side effects of antiarrhythmic drugs and to be aware of potential drug-drug interactions. Although fluoxetine was the drug used in this case, both duloxetine and paroxetine also cause potent inhibition of CYP2D6. Given this knowledge of drug-drug interactions, flecainide could have been started at a lower dose in this case or the patient could have been switch to another selective serotonin reuptake inhibitor that does not inhibit CYP2D6 to reduce the chance of side effects.[10]

Conclusion

Although the mechanism is unknown, it is important to be aware that encephalopathy is a rare but serious side effect of flecainide and can resolve with cessation of therapy. Flecainide is metabolized by the cytochrome P450 system and providers need to be cognizant that medications such as fluoxetine affect the cytochrome P450 system, leading to changes in the normal metabolism of flecainide. Given the prevalence of psychiatric medication use and antiarrhythmic drugs, providers must be aware of the drug-drug interactions psychiatric medications can have with antiarrhythmic drugs and use this as guidance for careful selection and dosing of medications.

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