Flecainide toxicity in renal failure

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ABSTRACT

Flecainide, a class Ic antiarrhythmic, is used for the prevention of paroxysmal supraventricular tachycardia, paroxysmal atrial fibrillation/flutter, and sustained ventricular tachycardia. Flecainide is primarily metabolized by the liver and to a lesser extent (30%) is excreted unchanged in the kidney. We present a case of flecainide toxicity in the setting of renal impairment that was successfully treated with intravenous sodium bicarbonate.

KEYWORDS Flecainide toxicity; renal failure; ventricular tachycardia

Flecainide, a Vaughan Williams class Ic antiarrhythmic, is approved by the Food and Drug Administration for the prevention of paroxysmal atrial fibrillation/flutter, sustained ventricular tachycardia, paroxysmal supraventricular tachycardia including atrioventricular nodal tachycardia, atrioventricular reentrant tachycardia, and other supraventricular tachycardia in patients without structural heart disease.^{1–3} It prolongs the depolarization phase of cardiac action potential by inhibiting the sodium channel and slows down the intracardiac conduction in all parts of the heart, with the greatest effect on the Purkinje-His system. It is primarily metabolized by the liver, and up to 30% is excreted unchanged by the kidney. Therefore, in a patient with renal impairment receiving a higher dose of flecainide, even in the setting of normal liver function, the drug may rapidly accumulate, causing the potential for acute flecainide toxicity. Here we present a case of flecainide toxicity in the setting of renal impairment that was successfully treated with intravenous sodium bicarbonate infusion.

CASE DESCRIPTION

A 44-year-old woman with a body mass index of 47 kg/m² was admitted for progressive dyspnea and lower-extremity edema. She had obstructive sleep apnea, heart failure with preserved ejection fraction, paroxysmal atrial fibrillation treated with a maze procedure, and a history of mitral and tricuspid valve repair. For sinus rhythm maintenance, she was taking flecainide 150 mg twice daily and metoprolol. Vital signs revealed a blood pressure of 102/62 mm Hg, heart rate of 62 beats per minute, and respiratory rate

of 26 breaths per minute. Physical examination showed elevated jugular venous pulse, bilateral pitting pedal edema, and bilateral pulmonary crackles. Laboratory analysis showed a blood urea nitrogen of 23 mg/dL, creatinine of 2.53 mg/dL (baseline 0.8 mg/dL), aspartate transaminase of 13 U/L, and alanine transaminase of 18 U/L. Fractional excretion of sodium was 0.1%, suggesting a renal hypoperfusion state. The electrocardiogram on admission showed sinus rhythm with a PR interval of 212 milliseconds and a QRS duration of 112 milliseconds. An echocardiogram showed an ejection fraction of 55% with grade II left ventricular diastolic dysfunction. The patient was treated with intravenous furosemide at 2.5 mg an hour. She subsequently became hypotensive and was transferred to the intensive care unit. At this time, medication included flecainide, which was continued at a dosage of 150 mg twice daily.

Ten days into her admission, she went into pulseless wide complex tachycardia and was successfully resuscitated after cardiopulmonary resuscitation. An electrocardiogram showed that her initial rhythm was atypical atrial flutter with an excessively wide QRS complex of 280 milliseconds, and QRS morphology (lead aVR) was suggestive of potential flecainide toxicity (*Figure 1a*). Electrolytes were normal, with a potassium level of 3.9 mEq/L and magnesium level of 2.3 mg/dL; pH was 7.39 in arterial blood gas. Review of her medications revealed that the dosage of flecainide (150 mg twice a day) was not adjusted based on renal function since admission. Flecainide was discontinued, and the patient was treated with a continuous sodium bicarbonate infusion to keep her pH between 7.50 and 7.55 for 48 hours. She

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Figure 1. Electrocardiograms (a) 10 days after admission showing atypical atrial flutter with a wide QRS complex of 280 milliseconds and (b) 2 days later, after treatment, showing atypical atrial flutter with normalization of the QRS complex with a QRS duration of 100 milliseconds.

received a total dose of 925 mEq of sodium bicarbonate over 48 hours. A repeat electrocardiogram after treatment showed normalization of the QRS complex, with a QRS duration of 100 milliseconds and atypical atrial flutter (*Figure 1b*). Resolution of wide QRS morphology with discontinuation of flecainide and treatment with sodium bicarbonate strongly suggested flecainide toxicity. Her renal function normalized, and metoprolol was resumed for rate control.

DISCUSSION

Flecainide is approved by the Food and Drug Administration for the prevention of paroxysmal supraventricular tachycardia, paroxysmal atrial fibrillation/flutter, and sustained ventricular tachycardia.^{1–3} However, use of flecainide has been limited because of its proarrhythmic effects and increase in mortality in patients with prior myocardial infarction, structural heart disease, and left ventricular

dysfunction.^{3,4} Because of its negative inotropic effect, it may cause or worsen congestive heart failure, particularly in patients with cardiomyopathy, preexisting severe heart failure (New York Heart Association functional class III or IV), or an ejection fraction <30%.³ Flecainide is primarily metabolized by the hepatic cytochrome P450 CYP2D6 system; however, approximately 30% of an oral dose is excreted in urine as unchanged drug.^{5–9} Though the elimination half-life of flecainide ranges from 7 to 23 hours, in patients with renal impairment it can be prolonged to 58 hours, and the total clearance of this drug might fall by approximately 40%.^{5–7} Therefore, the recommended starting dose is 100 mg daily or 50 mg twice a day in those with a creatinine clearance ≤ 35 mL/min/1.73 m². Whenever feasible, plasma flecainide levels should be monitored to keep the trough plasma level from <0.7 to 1 μ g/mL.³ Our patient continued to receive flecainide 150 mg twice a

day without any adjustment for her renal function. In addition, the failure to monitor the plasma flecainide level might have contributed to her adverse outcomes.

Flecainide toxicity manifests on the electrocardiogram similar to tricyclic antidepressant toxicity, because both are sodium channel inhibitors. It causes PR interval prolongation, widening of QRS, and first- and second-degree atrioventricular block.^{6,10} The QT interval may prolong as a concomitant effect of the QRS widening.^{9,11} Toxicity is suspected when the QRS duration increases by 50% or the PR interval is prolonged by 30%.¹¹ A prominent R wave (amplitude ≥ 3 mm) and an R wave to S wave ratio ≥ 0.7 in lead aVR are the most sensitive predictors of arrhythmias or seizures in patients with tricyclic antidepressant overdoses,^{12,13} which may help in diagnosing flecainide toxicity.

Flecainide toxicity is treated in the same manner as a tricyclic antidepressant overdose. Sodium bicarbonate is administered either as a continuous infusion or intermittent boluses to maintain the pH between 7.5 and 7.55 to reverse the action of sodium channel blockade.^{11,14–16} Sodium bicarbonate provides an increased sodium load, because hyponatremia may increase the potential for flecainide toxicity. In addition, alkalinization with sodium bicarbonate decreases the active ionized flecainide available for sodium channel inhibition.¹⁴ Intravenous fat emulsion therapy has also been shown to treat life-threatening ventricular arrhythmia caused by flecainide toxicity. It drives the offending drugs from the target tissue (site of toxicity) to the newly formed lipid sink.^{17,18}

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