Unusual severe hemodynamic failure associated with standard dose of intravenous flecainide for pharmacological cardioversion of atrial fibrillation

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Introduction

Flecainide is a Vaughan Williams class IC antiarrhythmic drug.[1] It produces an independent voltage and frequency inhibition of cardiac sodium channels to prolong cardiac action potential (slow the conduction of cardiac electrical signals) and is thus effective in supraventricular and ventricular arrhythmias.[2] The drug is clinically used for pharmacological cardioversion of atrial fibrillation (AF),[1] both intravenously and orally (so-called "pill-off-the-pocket" therapy[3]), and can also be used for prevention of arrhythmia recurrence. Its use is basically restricted to patients without structural heart disease.[4] Particularly it is contraindicated in patients with stenotic coronary artery disease and/or myocardial ischemia and those with severe left ventricular (LV) dysfunction and/or congestive heart failure. Several side effects, such as negative inotropy and facilitation of AV conduction, need to be considered; however, the overall safety-risk profile is very good.[1] Most physicians consider to give it with co-medication of ß-blocker therapy.

Case report

A 60-year-old man with a history of paroxysmal AF (PAF) since 2011 presented with an acute attack of PAF in August 2016. He was on chronic medication with metoprolol succinate 47.5 mg per day and rivaroxaban 20 mg per day for oral anticoagulation. He had a history of borderline hypertension without LV hypertrophy (septal wall thickness 11 mm), and obstructive bronchitis. He also had a history of episodic orthostatic intolerance, most probably owing to vasovagal reactions, of which symptoms and rare syncopal episodes had occurred during adolescence. His CHA2DS2-VASc score was 1. Echocardiography during tachyarrhythmia indicated a normal ejection fraction of 63%, grade I diastolic dysfunction, and no hemodynamic or structural heart diseases. Because the duration of the PAF was less than 12 hours, and the patient was on ß-blocker and continued oral anticoagulation therapy, immediate pharmacologic cardioversion using flecainide was offered, to which the patient agreed. An intravenous (IV) line was installed and continuous electrocardiography (ECG) monitoring (and recording) was initiated. The patient then received an IV infusion of flecainide 1 mg/kg over 5 minutes, and after 25 minutes another dose of 0.3 mg/kg flecainide.

After 30 minutes, he developed a very short episode of atrial flutter before converting to normal sinus rhythm (SR). Three minutes after being in SR, he reported feeling unwell and lightheaded, and rapidly developed circulatory depression. His blood pressure dropped to 60/40 mm Hg and he developed bradycardia with a heart rate of $\leq$30 beats per minute. Figure 1 depicts the patient's initial ECG (A) and the ECG during hemodynamic failure (B). The patient became presyncopal and cyanotic. Although immediate volume supplementation was initiated and the patient was brought into a "leg-up – head-down" position, hemodynamic stabilization could only be achieved by IV injection of 1 mg atropine and fractionated injection of 400 µg adrenaline. After 15 minutes, complete hemodynamic stabilization was achieved; however, it was decided to observe the patient for another 12 hours and he was thus transferred to a monitoring unit from where he was later discharged without any further complications.

Because the patient had no cardiovascular risk or LV dysfunction that may have indicated a predisposition to hemodynamic compromise, and because the dose of flecainide administered was less than the maximally allowed weight-adapted dose, we asked the manufacturer of the drug to examine the content of the special charge of ampulla of the drug that we had used. It was confirmed that the ampullas contained the appropriate dose of flecainide.

Further interrogation of the patient after the event revealed that the patient had not taken much fluid during the hours preceding the attack; more importantly—as outlined above—he had a history of orthostatic intolerance and fainting. However, the patient had been free of severe orthostatic intolerance for years. It can be hypothesized that the short episode of atrial flutter with high heart rate prior to conversion into SR in the setting of hypovolemia may have induced a vasovagal reflex with sympathetic withdrawal and bradycardia that, in

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KEY TEACHING POINTS

- Hemodynamic collapse following intravenous therapy of flecainide for pharmacological cardioversion of atrial fibrillation (AF) is a rare phenomenon in patients with no structural heart disease.
- Patients prone to vasovagal reflex syncope may be at higher risk of hemodynamic instability because the negative inotropic effects of flecainide may aggravate a reflex vasovagal reaction.
- Pharmacological cardioversion of AF should be guided under monitoring conditions with the ability to apply emergency medical therapy. Particular attention and possibly prolonged monitoring after conversion should be offered to patients with a history of reflex orthostatic or vasovagal reactions.

conjunction with an ongoing negative inotropic state following flecainide infusion, resulted in this unusually rapid circulatory deterioration, which could only be managed by injection of adrenaline.

Discussion

The use of flecainide for cardioversion of PAF is characterized by a good risk-safety profile; however, proarrhythmia and hemodynamic compromise are known side effects. Therefore, flecainide must be tested in an individual patient once under monitoring conditions, before prescribing the drug for self-medication ("pill-off-the-pocket"). Severe hemodynamic collapse—even resulting in resuscitation—has so far only been reported in cases of accidental or suicidal application of high overdoses of flecainide; a reduced LV function may also be a risk factor.[5,6] IV flecainide induces a mild to moderate but significant negative inotropic effect, which usually may be clinically significant for patients with an underlying LV dysfunction.[6] Flecainide can also cause

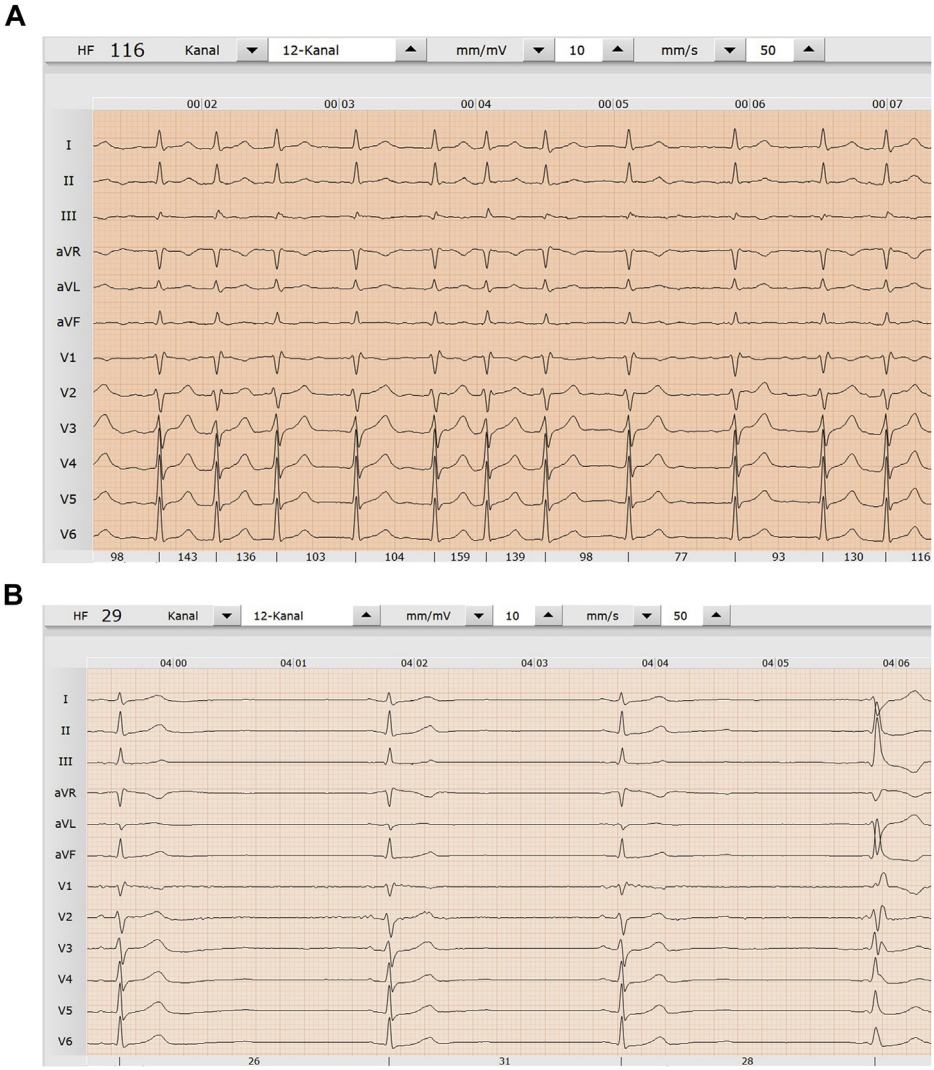

Figure 1 Twelve-lead electrocardiogram of the patient before administration of flecainide (**A**) and 3 minutes after cardioversion in sinus rhythm (**B**).

proarrhythmia.[7] Also, a Brugada-like electrocardiographic pattern can be induced by the drug.[8]

To our knowledge, we report here the first case of unusually severe hemodynamic collapse following administration of standard-dose IV flecainide for pharmacological cardioversion for AF in an otherwise healthy individual. IV flecainide rarely causes severe circulatory depression in patients with no structural heart disease.[2] Instead, hemodynamic failure is usually associated with overdose, co-medication with other antiarrhythmic drugs, or electrolyte disorders, or may occur in patients having atrial flutter of 1:1 ventricular conduction[2]—all of which were not present in this case.

Because the patient had a history of orthostatic intolerance, one likely explanation of the event is an unfavorable combination of an evolving vasovagal reflex with the ongoing negative-inotropic state following flecainide infusion, resulting in accelerating hemodynamic collapse that could only be managed by IV treatment with positive inotropic adrenaline. This case underlines that particular attention should be paid if IV flecainide is administered in patients with a history of orthostatic intolerance.

Conclusion

IV flecainide–induced hemodynamic failure is a very rare complication in pharmacological cardioversion of AF patients with no structural heart disease. The likely cause of hemodynamic failure in the present case is a combined-reflex vasovagal reaction amplifying the negative inotropic effect of the drug.

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