CASE REPORT

Flecainide associated torsade de pointes: A potential case of reverse use dependence

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Flecainide has been known to cause torsades de pointes (TdP) in patients with structural heart disease and its mechanism has been attributed to use-dependency. We present a patient with flecainide-induced TdP in the absence of any other precipitating factors. This case highlights potential reverse use dependence associated with flecainide resulting in TdP.

Key words: Arrhythmias, clinical electrophysiology, drugs, electrophysiology, receptor pharmacology

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INTRODUCTION

Since inception, numerous side effects have been attributed to anti-arrythmic medications.[1,2] Torsades de pointes (TdP) is a potentially fatal ventricular dysrrhythmia that is characterized by QRS complexes of variable amplitude and an axis that appear to twist around an isoelectric baseline with a ventricular rate of 200-250 beats/min.[3] Medications are commonly implicated as the primary etiology of TdP, and in particular the Class Ia and Class III anti-arrhythmics are commonly reported as the precipitant.[4]

We present a patient with a potential reverse use dependence associated with flecainide resulting in TdP in the absence of any other precipitating factor.

CASE REPORT

A 69-year-old woman with a past medical history of hypertension and symptomatic paroxysmal atrial fibrillation presented to the emergency department with altered mental status that occurred on past two nights. She described awakening during the night after wetting her bed and feeling paralyzed. Her husband noticed her "thrashing around the bed with garbled speech" and activated emergency medical service.

Her home medications had been lisinopril 2.5 mg twice a day, flecainide 150 mg twice a day, dabigatran 150 mg twice a day, digoxin 0.125 mg daily and diltiazem CD 120 mg daily. Her digoxin and diltiazem were discontinued recently due to symptomatic sinus bradycardia. Transthoracic echocardiogram showed a structurally normal heart and a recent nuclear stress test was negative for perfusion defect.

At the time of admission the physical exam was significant for bradycardia at a rate of 50 beats/min with otherwise normal vital signs. She had no focal neurological deficits and her cardiac exam was normal. Laboratory evaluation exhibited normal basic metabolic panel, thyroid function tests, blood counts, urine and serum drug screen. Electro cardiogram (ECG) demonstrated sinus bradycardia at a rate of 49 beats/min, first degree AV block (PR interval 272 ms), and QT prolongation (QTc 506 ms). QRS duration was 100 ms.

Shortly after admission she had a cardiac arrest. She was successfully resuscitated after 2 rounds of external defibrillation. A telemetry rhythm strip at the time of the event showed non-sustained ventricular tachycardia (VT) with "R on T" phenomenon leading to polymorphic VT in a TdP pattern followed by ventricular fibrillation [Figure 1]. ECG after her resuscitation demonstrated sinus bradycardia, QT prolongation (QTc 546 ms) and QRS widening (160 ms). The patient underwent coronary angiography, which showed normal epicardial arteries.

Flecainide was discontinued and intravenous lidocaine was started. She underwent placement of a dual-chamber intracardiac defibrillator and her atrial pacing rate was set to 80 beats/min. Due to previous side effects,

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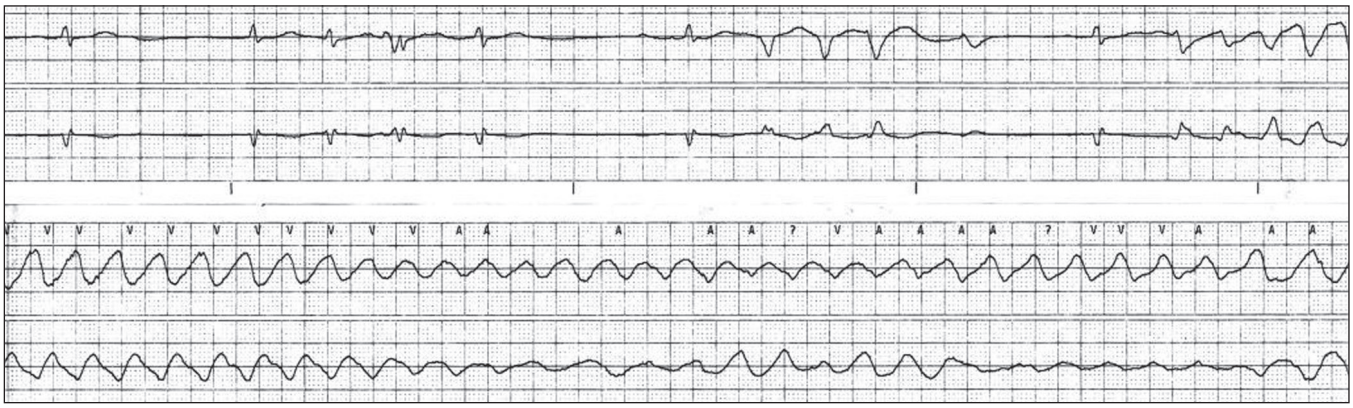

Figure 1: Continuous telemetry strip from the time of her arrest (leads II and V). Note the bradycardia followed by ventricular dys-rhythmia with the first few complexes positive in lead V then becoming negative in a "twisting of the points" pattern

the patient was unable to tolerate amiodarone or sotalol. As the patient was very symptomatic during atrial fibrillation, a rhythm control strategy with flecainide and diltiazem was utilized. Prior to discharge, she was monitored in the hospital for 3 additional days after restarting flecainide and there was no recurrence of her arrhythmia. At a 6-week ICD interrogation appointment, she was in stable condition and had no arrhythmia.

DISCUSSION

We present a patient with sinus bradycardia and TdP in the setting of maximum dose of flecainide for atrial fibrillation and in the absence of any electrolyte abnormality or structural abnormality in the heart.

Flecainide acts by blocking fast inward sodium channels and its anti-arrhythmic effect is secondary to depression of the cardiac action potential upstroke.[5] Drug binding and efficacy increases as the heart rate increases in the so-called "use dependence" pattern. Due to this pharmacologic property, flecainide is known to be much more active in tachyarrhythmias when compared to bradyarrhythmias.[6] It is possible that the degeneration of VT into ventricular fibrillation was catalyzed by flecainide's use dependence pharmacokinetics.

Significant side effects of flecainide include sinus node dys-function, AV block, and QT prolongation. The pro-arrhythmic potential of flecainide via the QT prolonging effects are thought to be due to blocking of I_{Kr} channels in the ventricular myocytes.[7] Animal models have demonstrated that flecainide exclusively decreases I_{Kr} activity in a "reverse-use dependence" pattern.[8,9] Although Class Ic drugs were implicated as pro-arrhythmic in the CAST trial,[10] ventricular arrhythmias, such as TdP are rarely described in patients with structurally normal hearts.

This case highlights a potential reverse use dependence associated with flecainide resulting in TdP.

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REFERENCES

1. Wooten JM, Earnest J, Reyes J. Review of common adverse effects of selected antiarrhythmic drugs. Crit Care Nurs Q 2000;22:23-38.
2. Singla S, Strobel AL, Deshmukh AJ, Paydak H. Amiodarone-Related Hyponatremia: Rare but Potentially Lethal. Am J Ther 2011Feb 10. [Epub ahead of print]
3. Dessertenne F. Ventricular tachycardia with 2 variable opposing foci. Arch Mal Coeur Vaiss 1966;59:263-72.
4. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, *et al*. Prevention of torsade de pointes in hospital settings: A scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2010;55:934-47.
5. Falk RH, Fogel RI. Flecainide. J Cardiovasc Electrophysiol 1994;5:964-81.
6. Wang Z, Fermini B, Nattel S. Mechanism of flecainide's rate-dependent actions on action potential duration in canine atrial tissue. J Pharmacol Exp Ther 1993;267:575-81.
7. Follmer CH, Colatsky TJ. Block of delayed rectifier potassium current, IK, by flecainide and E-4031 in cat ventricular myocytes. Circulation 1990;82:289-93.
8. Langenfeld H, Köhler C, Weirich J, Kirstein M, Kochsiek K. Reverse use dependence of antiarrhythmic class Ia, Ib, and Ic: Effects of drugs on the action potential duration? Pacing Clin Electrophysiol 1992;15:2097-102.
9. Wang DW, Kiyosue T, Sato T, Arita M. Comparison of the effects of class I anti-arrhythmic drugs, cibenzoline, mexiletine and flecainide, on the delayed rectifier K+ current of guinea-pig ventricular myocytes. J Mol Cell Cardiol 1996;28:893-903.
10. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, *et al*. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781-8.

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