

A Case Series of Sotalol-induced Torsade de Pointes in Patients with Atrial Fibrillation – A Tale with a Twist

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Abstract

Introduction: Sotalol is a potent antiarrhythmic often used in patients with atrial fibrillation. However, it has been associated with a risk of provoking other potentially dangerous arrhythmias, especially if used in high doses and in patients with uncorrected electrolyte imbalance or impaired renal and cardiac function. **Clinical Picture:** We present 4 patients with atrial fibrillation treated with sotalol who developed torsade de pointes due to marked prolongation of the QT interval. While 1 patient had renal failure, all had normal left ventricular function. One patient had been treated with sotalol for more than 10 months before developing torsade de pointes precipitated by hypokalaemia, while another had tolerated sotalol for a 3-month period before the drug was discontinued, and only developed torsade de pointes when the drug was restarted 2 years later. Significantly, the doses used in all patients were relatively low, in contrast to most other reported cases where higher doses were used. **Conclusion:** As with all antiarrhythmic therapy, these cases illustrate the need for close follow-up of patients treated with sotalol, even if relatively low doses are used. In addition, patients who had previously tolerated the drug well are still susceptible to its proarrhythmic effects.

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Key words: Atrial fibrillation, QT interval, Sotalol, Torsade de pointes

Introduction

In the light of the Cardiac Arrhythmia Suppression Trial (CAST) which suggested that class I antiarrhythmics may be linked to an increase in mortality,¹ attention has been turned towards the use of class III drugs for the management of both atrial and ventricular arrhythmias. While the adverse effects of amiodarone are numerous and multi-systemic, those of sotalol are few and mainly cardiac. This has resulted in increasing use of the drug, even though it is known to carry a substantial risk of proarrhythmia, especially that of torsade de pointes. This is aggravated in the presence of renal impairment, bradycardia, electrolyte imbalance, poor left ventricular function, a lengthened QT interval and higher doses (especially if >320 mg per day).²

We present 4 patients with atrial fibrillation (AF) who were treated with oral sotalol, and who subsequently developed torsade de pointes. All 4 patients were female and all had normal left ventricular function and QT intervals at the start of treatment.

Case Reports

The significant features of all 4 cases are summarised in Table I.

Case 1

A 70-year-old Chinese woman with a history of rheumatic mitral valve disease as well as ischaemic heart disease and paroxysmal AF was admitted with the complaint of palpitations. She was found to be in AF with a rapid ventricular response of 160 to 170 beats per minute. She was given a 5 mg intravenous dose of verapamil, after which she reverted to sinus rhythm. She was then started on oral sotalol 80 mg twice a day for maintenance of sinus rhythm. She was on sotalol for 8 days (cumulative dose, 1280 mg) before undergoing mitral valve replacement with concomitant coronary artery bypass surgery. Sotalol was stopped on the day of surgery. However, 5 days postoperatively, she developed AF again and sotalol was restarted at a dose of 40 mg twice daily. Her serum

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TABLE 1: CHARACTERISTICS OF PATIENTS WITH SOTALOL-INDUCED TORSADE DE POINTES

Case	Age (y)	Diagnosis	Concomitant disorders	LVEF	Sotalol dose (mg)		QT before sotalol		QT with sotalol		Outcome
					Daily	Cumulative	QT (ms)	QTc (ms)	QT (ms)	QTc (ms)	
1	70	RHD	-	52%	160	1440	461	465	580	508	Survived
2	86	IHD	Renal failure	55%	160	160	320	472	640	628	Survived
3	63	RHD	-	60%	240	-	440	440	560	583	Survived
4	67	MVP	-	60%	160	560	400	471	620	556	Survived

IHD: ischaemic heart disease; LVEF: left ventricular ejection fraction; MVP: mitral valve prolapse; QT: QT interval; QTc: rate-corrected QT interval; RHD: rheumatic heart disease

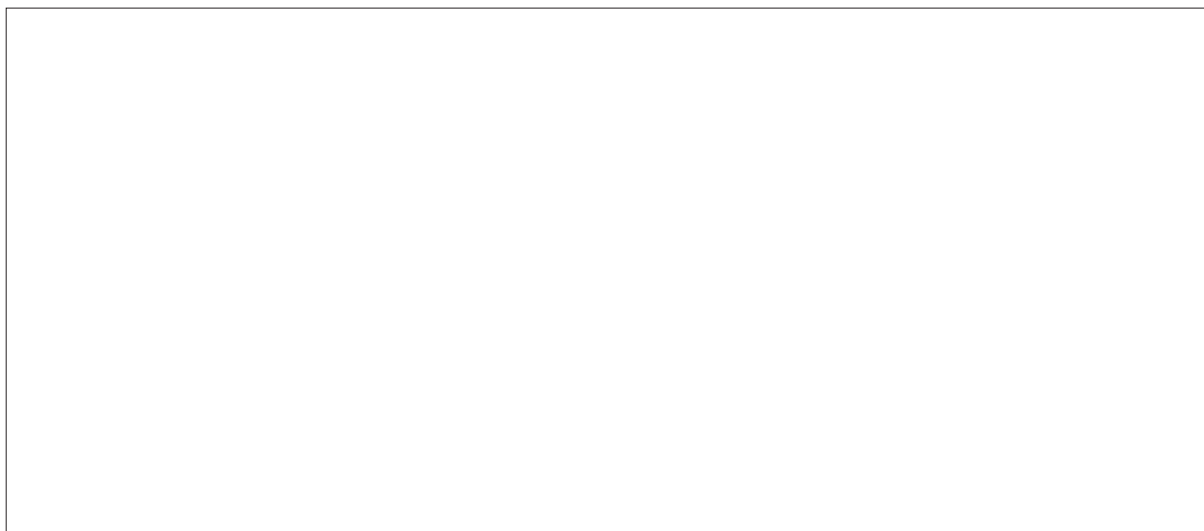


Fig. 1. Electrocardiogram of case 1 showing atrial fibrillation with a heart rate of 48 beats per minute and prolonged QT interval.



Fig. 2. Electrocardiogram tracing of case 1 with torsade de pointes.

creatinine and electrolytes were normal, as was her left ventricular function. Two days later, an electrocardiogram (ECG) showed AF with a heart rate of 48 beats per minute and a prolonged QT interval of 580 ms. The rate-corrected QT (QTc) interval was 508 ms (Fig. 1). Although sotalol was withdrawn, she developed torsade de pointes later that day (Fig. 2). She was treated successfully with intravenous magnesium and temporary ventricular overdrive pacing.

Case 2

An 86-year-old Chinese woman with a history of

ischaemic heart disease and triple vessel disease treated medically was admitted for dyspnoea. She also had end-stage renal failure requiring haemodialysis. She was found to have AF, which was not present at her last clinic visit. She was not in heart failure and echocardiography showed normal left ventricular function. Her serum electrolytes were normal. She was commenced on sotalol 80 mg twice daily. The following day, after a cumulative dose of only 160 mg, she developed a grossly prolonged QTc interval (628 ms) and torsade de pointes, requiring treatment with lignocaine and magnesium.

Case 3

A 63-year-old Chinese woman with a history of rheumatic mitral valve disease and normal left ventricular function was initially commenced on amiodarone for chronic AF. However, she was found to have eye deposits, and therapy was changed to sotalol. She was started on 80 mg twice daily and the dose was increased to 120 mg twice daily after 2 months. Her serum creatinine and electrolytes were normal and she was well on initial outpatient follow-up. However, 10 months later, she was admitted with torsade de pointes which required treatment with lignocaine, magnesium and temporary transvenous overdrive pacing. She was found to have a markedly prolonged QTc interval (583 ms) and was hypokalaemic (serum potassium 2.9 mmol/L). She subsequently developed incessant atrial flutter and sick-sinus syndrome, requiring atrioventricular nodal ablation and permanent pacemaker implantation.

Case 4

A 67-year-old Chinese woman with a history of mitral valve prolapse and adequately treated Grave's disease was evaluated at the outpatient clinic for the complaint of intermittent palpitations. She was found to have paroxysmal AF and was commenced on sotalol 80 mg twice daily. After 3 months, she was asymptomatic and the sotalol was stopped. At that time, there was no significant prolongation of the QT intervals on her ECG. Two years later, she was admitted with symptomatic AF due to rapid ventricular response. She was started on sotalol 40 mg twice a day and cardioversion was successfully performed with reversion to sinus rhythm, whereupon sotalol was stopped. Three days later, AF recurred again and sotalol was restarted at a dose of 80 mg twice daily. After 3 days (and a cumulative dose of 560 mg), she developed torsade de pointes, requiring electrical cardioversion and treatment with intravenous lignocaine, magnesium and temporary transvenous overdrive pacing. All electrolytes were within normal ranges at the time. An ECG revealed a prolonged QTc interval of 556 ms.

Discussion

This is the first locally reported case series of sotalol-induced torsade de pointes, although this proarrhythmic propensity of sotalol has been well reported in many clinical trials.^{3,4} Except for female gender, renal failure (case 2) and hypokalaemia (case 3), none of the other known predisposing risk factors were present. All our patients had normal left ventricular function and there had been no concomitant administration of medications known to prolong the QT interval such as tricyclic anti-depressants, certain antibiotics, especially the macrolides, the newer anti-histamines and other antiarrhythmic drugs. The significant feature in these patients is the development of

torsade de pointes with relatively low doses of sotalol, ranging from 80 to 240 mg daily, in contrast to most other reported cases in which the arrhythmia occurred with higher doses.

Sotalol was studied and marketed in Europe as an anti-hypertensive agent as early as the 1970s, and interest in sotalol's unique antiarrhythmic properties arose only in the early 1980s.⁵ By 1992, the Food and Drug Administration (FDA) had approved its usage in life-threatening arrhythmias in the United States. However, sotalol has also been promising in its efficacy in terminating and preventing supraventricular tachyarrhythmias. In Benditt and colleagues' randomised, double-blind, multi-centre trial,⁶ 253 patients were assigned to various sotalol drug dosage groups (80, 120 and 160 mg twice daily) to study the efficacy, safety and dose response to the use of sotalol in maintaining sinus rhythm of patients with AF or atrial flutter. The time to first recurrence of atrial arrhythmias was found to be dose-dependent, with the dose of 120 mg twice a day providing the best benefit-risk ratio. Interestingly, the study did not report any deaths or serious arrhythmic episodes, including torsade de pointes. In Joseph and Ward's study of 120 patients with new-onset AF of less than 24 hours' duration,⁷ subjects were randomly assigned to treatment with sotalol, amiodarone or digoxin. There was a significant reduction in time to reversion with both sotalol and amiodarone, as compared to digoxin. Furthermore, in patients who remained in AF, there was superior ventricular rate control in the sotalol group. Trials in the use of sotalol to prevent AF and supraventricular arrhythmias in patients undergoing coronary artery bypass surgery have also shown sotalol to be beneficial in comparison to controls or placebos.^{8,9} As a result, sotalol is now a widely prescribed drug for both ventricular and atrial arrhythmias in many parts of the world, including Southeast Asia. From pharmacy records over a 4-year period from June 1998 to May 2002, sotalol was dispensed to about 230 patients per year in our institution, with doses ranging from 80 to 320 mg daily. The most frequent daily dosage was 160 mg.

The clinical pharmacokinetics of sotalol are well defined.¹⁰ The bioavailability of the drug is high, with near-complete absorption after oral administration and it has no significant first pass metabolism. Hence, although available in both oral and intravenous forms, oral administration is usually preferred. Peak plasma concentrations occur 2 to 4 hours after oral dosing and the terminal elimination half-life is between 10 and 20 hours. Approximately 80% to 90% of the drug is excreted unchanged in the urine. Thus, the drug accumulates in patients with renal impairment, necessitating adjustments in its dosing intervals in such patients. In patients with normal renal function, steady state plasma concentration of the drug is reached within 3 days, and plasma levels vary linearly with dose.¹¹

It has been established that the risk of inducing serious proarrhythmias is proportional to the dose and would be substantially raised for daily dosages of more than 320 mg. In a report on the clinical safety profile of sotalol in 3257 patients,² the incidence of serious arrhythmias was 0% for a daily dose of 80 mg, 0.5% for 160 mg and 1.8% in subjects treated with doses between 160 mg and 320 mg per day. In those treated with 480 mg per day, the risk increased drastically to 4.5%, and at doses of more than 640 mg per day, the risk was even higher, at 6.8%. In our patients, the highest daily dose prescribed was only 240 mg, which was well below the dose limit of 320 mg where there is a sharp increase in the risk of proarrhythmia. Previously reported cases usually received higher doses compared to our patients, and patients who were reported to develop torsade de pointes at low doses were suffering from renal failure.¹² This is illustrated by case 2, where the arrhythmia developed only 1 day after starting sotalol, with a cumulative administered dose of only 160 mg.

The fact that all our 4 cases were female patients came as no surprise, given that women have been reported to have an increased risk of developing torsade de pointes. In Makkar et al's study involving 332 subjects, the female gender was identified as a risk factor for sotalol-induced torsade de pointes.¹³ In a follow-up study derived from 22 clinical trials involving 3135 patients who received oral sotalol, the incidence of torsade de pointes was 4.1% for women and 1.9% for men ($P < 0.001$).¹⁴ Logistic regression analysis also identified the following as predictors of torsade de pointes in decreasing order of importance: female gender, sustained ventricular tachycardia or fibrillation, history of congestive cardiac failure and sotalol dosage >320 mg/dL. In addition, an elevated baseline serum creatinine level was found to be weakly predictive. After adjustment for these risk factors, female gender was established to have a three-fold greater risk of developing torsade de pointes than men. The reason for this is not apparent, although the findings could be due to women displaying longer average QTc intervals than men.¹⁵

In case 1, the QTc interval was 508 ms, which was significantly less than the markedly prolonged QT interval (Table I). This is due to bradycardia and is a clear illustration of how a predisposing factor for torsade de pointes (QT prolongation) can be masked by another (bradycardia).¹⁶ In addition, QT interval prolongation by sotalol has been shown to be rate-dependent, being more marked with slower heart rates.¹⁷ Though it is usual to depend on the QTc interval for monitoring patients on sotalol therapy, the absolute QT duration is also an important parameter, especially in the presence of bradycardia, which is often seen in such patients.

Our cases also illustrate that the time from commencement of drug therapy to the onset of torsade de pointes is highly variable and indicative of the idiosyncratic nature of the proarrhythmic risk. In case 1, sotalol, which had been well tolerated initially, was stopped for 5 days before resumption at a lower dose; this led to the arrhythmic episode. Case 3 was treated with sotalol for more than 10 months before an episode of hypokalaemia precipitated the arrhythmic event; while in case 4, sotalol, which had been utilised safely for a short period, was restarted after a 2-year break. Hence, even though patients may have been treated safely with sotalol previously, close monitoring, especially for QT interval and serum electrolyte changes, is obviously still of paramount importance.

Previously published studies had advocated hospital admission for initiation of sotalol therapy based on the finding that clinically significant arrhythmias usually occurred within 3 to 7 days of starting therapy.^{5,14,18} However, as shown in our patients, the highly variable time from commencement of drug therapy to the onset of torsade de pointes, coupled with increasing hospitalisation costs, brings to light the difficulty in designing an optimal monitoring strategy for such patients. Extra caution should be paid to female patients, those with renal impairment or at risk of hypokalaemia, and therapy for these patients should be initiated in hospital under ECG monitoring if possible, with up to 72 hours of observation as suggested in existing publications.¹⁸

Conclusion

Though the efficacy of sotalol is well proven, it is important to keep in mind the risk of proarrhythmia. Accordingly, appropriate care must be exercised when starting patients on sotalol. It should be avoided in situations where QT prolongation is already present, or with uncorrected electrolyte imbalances such as hypokalaemia and hypomagnesaemia, which may augment QT prolongation. In addition, patients should not be prescribed with other medications with the potential to prolong the QT interval. Dose modification will also be important for patients with renal insufficiency, though as seen in our patients, the risk of torsade de pointes is still present even with low doses in patients with normal renal function. As such, close and careful follow-up of patients treated with sotalol is essential.

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