

# Sotalol, hypokalaemia, syncope, and torsade de pointes

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**SUMMARY** Thirteen patients developed syncope and a prolonged QTc interval while taking therapeutic doses of sotalol. Polymorphous ventricular tachycardia was observed in 12 patients, and criteria typical of torsade de pointes were present in 10. In 12 patients sotalol had been given with hydrochlorothiazide in a combined preparation, Sotazide, but with inadequate or no potassium supplementation. Serum potassium concentrations were reduced in eight patients. Four patients were taking other drugs known to prolong the QT interval, including disopyramide (three patients) and tricyclic antidepressants (two patients). The QT interval returned to normal in all patients after withdrawal of the drugs and correction of the hypokalaemia. Thus even in low dosage sotalol may be hazardous in the presence of hypokalaemia or when combined with drugs that also prolong the QT interval. The use of sotalol concurrently with potassium losing diuretics, such as the combined preparation Sotazide, may expose the patient to unnecessary risk and should be avoided unless the class III antiarrhythmic action of this unique beta adrenoreceptor blocking agent is also required.

Drugs that prolong the QT interval may cause life threatening ventricular arrhythmias, particularly of the torsade de pointes<sup>1,2</sup> or polymorphous ventricular tachycardia<sup>3</sup> variety. These have been reported in association with several of the class I antiarrhythmic drugs, such as quinidine,<sup>4</sup> procainamide,<sup>3,5</sup> and disopyramide.<sup>6,7</sup> Amiodarone, an antiarrhythmic drug that prolongs the QT interval by virtue of its class III properties, has also been associated with torsade de pointes.<sup>8</sup>

Over the past few years, interest has been shown in the class III antiarrhythmic action of the beta adrenergic blocking agent sotalol.<sup>9-11</sup> Evidence is accumulating that sotalol is a more effective antiarrhythmic agent than other beta blockers<sup>9,11,12</sup> and this has been attributed to its class III activity. Several reports,<sup>12-15</sup> however, have suggested that like other antiarrhythmic agents it may be arrhythmogenic. Elonen and associates<sup>15,16</sup> reported six cases of severe sotalol poisoning, all with considerable prolongation of the QT interval. Severe ventricular arrhythmias, including ventricular tachycardia and fibrillation, were

recorded in five of the six and correlated with the prolongation of the QT interval and the serum sotalol concentration. Ventricular tachyarrhythmias associated with a prolonged QT interval have also been reported in three patients taking large but therapeutic doses of sotalol;<sup>13,14</sup> in one of the three the tachycardia was typical of torsade de pointes.<sup>14</sup>

The present study reports 13 patients who developed a prolonged QT interval and syncope after taking relatively small therapeutic doses of sotalol.

## Patients and methods

### CLINICAL DATA

Between 1979 and 1983 13 patients, all but one of whom were female, developed syncope and a prolonged QT interval while taking sotalol (Table). The daily dose ranged from 80 to 480 mg. Twelve were being treated for hypertension (including one with frequent ventricular extrasystoles), and one (case 7) was taking sotalol and other agents for frequent ventricular extrasystoles associated with ischaemic heart disease. All but one of the 13 patients were taking the combined preparation Sotazide (sotalol hydrochloride 160 mg, hydrochlorothiazide 25 mg). One patient (case 1) had an episode of syncope within two hours of taking the first dose of Sotazide and five others (cases 3, 4, 7, 9, and 10) had syncope after taking Sotazide for 24

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Table Clinical, electrocardiographic features, and serum potassium concentrations in 13 patients with syncope

Case No	Age (yr) and sex	Treatment with sotalol			
		Indication	Daily dose mg <sup>a</sup>	Duration	Other treatment (daily dose)
1	55 F	Hypertension	160	2 h	
2	65 F	Hypertension	160	3 yr	
3	31 F	Hypertension	320	3 d	
4	70 F	Hypertension	160	1 d	Prednisone (50 mg); Azothiaprime (125 mg) Amitriptyline (75 mg); Imipramine (50 mg)
5	34 F	Hypertension	160	5 w	
6	67 F	Hypertension	320	3 m	Methyldopa (1000 mg); Hydralazine (150 mg); Frusemide (80 mg); Potassium chloride (3600 mg, 6 tabs)
7	75 F	Ventricular extrasystoles	480	2 d	Disopyramide (300 mg); Digoxin (0.25 mg); Prazosin (3 mg); Frusemide (120 mg); Potassium chloride (3600 mg)
8	72 M	Hypertension	320	1 yr	
9	38 F	Hypertension	320	3 d	Hydralazine (60 mg)
10	80 F	Hypertension	160	2 d	Imipramine (50 mg); Disopyramide (200 mg)
11	65 F	Hypertension	320	6 m	Methyldopa (750 mg)
12	66 F	Hypertension and ventricular extrasystoles	320	1 y	Disopyramide (300 mg)
13	75 F	Hypertension	80 (sotalol)	10 d	Hydralazine (30 mg); Moduretic (1 tablet daily)

\* Of Sotazide (sotalol hydrochloride 160 mg, hydrochlorothiazide 25 mg).

† Measured from Q to R wave.

‡ ECG not recorded daily.

§ Observed on ECG monitor.

Navidrex K, 0.25 mg cyclopenthiiazide with 600 mg potassium chloride.

Moduretic, amiloride hydrochloride 5 mg and hydrochlorothiazide 50 mg.

+, present; -, absent; T, torsades de pointes ventricular tachycardia; PVT, polymorphous ventricular tachycardia.

to 72 hours. Five patients had taken other diuretic agents before or together with Sotazide. Only three patients (cases 1, 6, and 7) were receiving potassium supplements. Three (cases 7, 10 and 12) were taking disopyramide, one of whom (case 10) was also taking imipramine. A further patient (case 4) was taking both imipramine and amitriptyline. Eight patients (Table) were hypokalaemic with serum potassium concentrations of less than 3.5 mmol/l. In one of these (case 2), the hypokalaemia was probably caused or increased by acute diarrhoea, whereas in the remainder, all but one (case 13) of whom were taking Sotazide, no predisposing factors were present other than diuretic therapy. Treatment with sotalol was stopped in all patients and potassium supplements given when indicated. The episodes of syncope and the ventricular arrhythmias ceased within 12 hours in all cases. The torsades de pointes was converted to sinus rhythm by cardioversion in our first patient (case 1). Four patients (cases 2, 5, 9, and 13) also received lignocaine which appeared to decrease, but did not abolish, the extrasystoles.

#### ELECTROCARDIOGRAPHIC DATA

##### QT interval

The QT interval was measured from the onset of the QRS complex to the end of the T wave. In one patient (case 10), in whom a constant bigeminal rhythm interrupted the T wave (Fig. 1), it was measured to the

QRS of the extrasystole. The corrected QT interval (QTc) was calculated using Bazett's formula.<sup>17</sup> In all 13 patients the QTc was prolonged and returned to normal within varying periods after sotalol treatment was stopped (Table).

##### Ventricular arrhythmias

Polymorphous ventricular tachycardia was recorded on the electrocardiogram in 11 patients (Table).

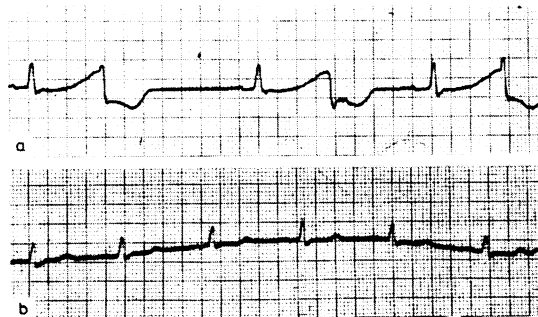


Fig. 1 Case 10: Electrocardiograms of an 80 year old woman on admission. (a) Lead I shows bigeminy with the extrasystoles occurring late but falling on the T wave; the QTc interval (measured from Q to R) is notably prolonged at 0.76 s. (b) The same lead recorded two days after withdrawal of Sotazide and other drugs shows a QTc interval of 0.41 s.

QTc interval (s)				Ventricular arrhythmia		
With sotalol	Without sotalol	Time when normal (days)	Serum potassium concentration (mmol/l)	T/PVT	Bigeminy	Other relevant factors
·60	0·42	7	3·6	T	—	Taking acebutolol 200 mg and Navidrex K1 tablet daily until Sotazide started
·58	0·38	2	3·4	T	+	Severe diarrhoea before syncope
·59	0·38	3‡	4·1	T	—	Sotazide started 2 days after renal transplantation
·59	0·39	2	3·2	T	+	Intermittent treatment with frusemide (self-prescribed for 9 months)
·60	0·40	30‡	3·8	T	+	
·58	0·42	3‡	3·1	T	+	
·64	0·40	2	2·0	T	—	Ischaemic heart disease Disopyramide started at same time as Sotazide
·64	0·44	1	3·8	PVT	+	
·62	0·40	3‡	2·5	T	—	Methyldopa and Navidrex K 2 tablets daily for 4 months until Sotazide started
·76†	0·41	2‡	3·1	—	+	Ischaemic heart disease
·60	0·38	2‡	2·1	T	+	
·59	0·42	7†	4·2	PVT§	—	Disopyramide started 2 weeks before syncope
·60	0·36	7	3·4	T	—	Extra dose of sotalol 160 mg given a few hours before syncope Mild renal failure

Ventricular tachycardia was observed on the monitor screen but was not recorded in another (case 12), whereas in the remaining patient (case 10), the 80 year old woman with a QTc of 0·76 s and a constant bigeminal rhythm (Fig. 1), the probability that a ventricular tachyarrhythmia was responsible for her syncope was never confirmed. Typical features of torsade de pointes were present in 10 of the 11 patients in whom ventricular tachycardia was recorded. We have used the term torsade de pointes, first described by Dessertenne<sup>1</sup> but clarified more recently by Krikler and Curry,<sup>2</sup> for paroxysms of ventricular tachycardia in which the QRS axis undulates over runs of 5 to 20 beats with changes in direction and with electrocardiographic evidence of prolonged repolarisation between episodes. A common finding, which occurred in seven patients, was ventricular bigeminy with broad bizarre ventricular extrasystoles. The coupling interval in these patients was prolonged and ranged from 0·60 to 0·75 s.

#### CASE REPORTS (TABLE)

*Case 1*—A 55 year old woman had been treated for hypertension for several years with acebutolol and Navidrex K (cyclopentiazide 250 µg and potassium 8·1 mmol). These drugs were then substituted with Sotazide. About two hours after taking the first tablet, she felt dizzy and had a syncopal attack lasting a few minutes. She had two further spells of loss of

consciousness, and on admission to hospital she was unconscious and torsade de pointes was present. After cardioversion the electrocardiogram showed a QTc interval of 0·60 s. The serum potassium concentration was 3·6 mmol/l. Treatment with Sotazide was stopped and seven days later the QTc interval was normal at 0·42 s. Two weeks later an electrophysiological study was performed, and ventricular tachycardia could not be initiated by stimulation of the right ventricle. The patient has remained asymptomatic for four years taking cyclopentiazide (Navidrex) one tablet daily.

*Case 4*—A 70 year old woman was receiving amitriptyline 75 mg daily and imipramine 50 mg at night. She had also been taking frusemide intermittently for ankle oedema. A regimen of one tablet daily of Sotazide was started for the treatment of mild hypertension. Three hours after taking the second tablet, she had a syncopal attack and was admitted to hospital where multiform ventricular extrasystoles and several spontaneously terminating runs of torsade de pointes were recorded (Fig. 2). The serum potassium concentration was 3·2 mmol/l and the QTc interval measured 0·59 s. After withdrawal of all treatment and replacement of potassium, the QTc interval returned to normal. She has had no further syncope or ventricular extrasystoles.

*Case 8*—A 72 year old man with hypertension had been taking Sotazide two tablets daily for a year. He was admitted to the intensive care unit after a syncopal

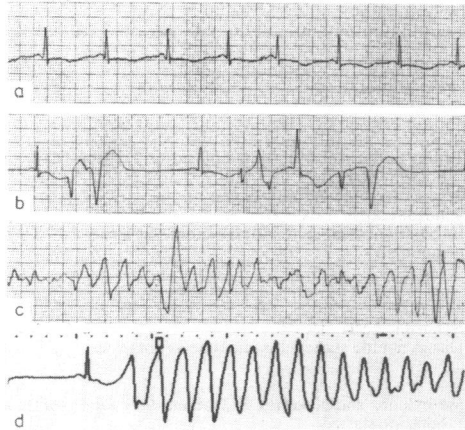


Fig. 2 Case 4: Electrocardiographic lead rhythm strips (modified lead II) of a 70 year old woman showing (a) QTc interval of 0.59 s; (b) multiform ventricular extrasystoles; and (c) and (d) runs of torsade de pointes; in (d) the tachycardia is initiated by an extrasystole.

attack and was found to have ventricular bigeminy (Fig. 3a) with frequent short runs of a polymorphous ventricular tachycardia (Fig. 3b and d). The QTc interval measured 0.64 s and the serum potassium concentration was 3.8 mmol/l. Treatment with Sotazide was stopped, and he was given potassium supplements. Within 24 hours the QTc interval was 0.44 s (Fig. 3c) and all ventricular arrhythmias had ceased.

**Case 9**—A 38 year old woman had been treated for hypertension with hydralazine, methyldopa, and cyclopentiazide (Navidrex) two tablets daily for four

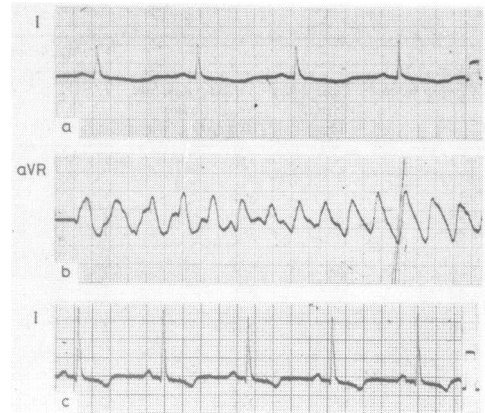


Fig. 4 Case 9: Electrocardiograms showing (a) prolonged QT interval (QTc = 0.62 s on lead I on admission); (b) torsade de pointes recorded in lead aVR; and (c) lead I recorded three days after withdrawal of Sotazide (QTc = 0.40 s).

months. Because of inadequate control, the latter two drugs were stopped and replaced by Sotazide in a dose of two tablets daily. Three days later, after a total of six tablets of Sotazide, she had syncope associated with palpitations and sweating. On admission the QTc interval was 0.62 s, and several self limiting runs of torsade de pointes were recorded (Fig. 4). During one prolonged episode she was given intravenous lignocaine. Her serum potassium concentration was 2.5 mmol/l. Treatment with Sotazide was stopped and the hypokalaemia corrected. Three days later an electrocardiogram showed a normal QTc interval of 0.40 s.

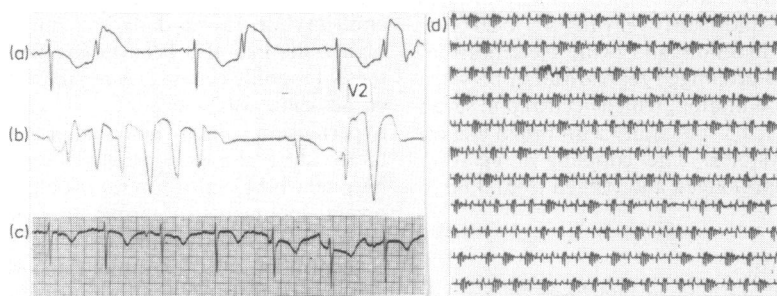


Fig. 3 Case 8: (a) Electrocardiogram (lead V2) on admission shows prolonged QTc interval (0.64 s) and bigeminal rhythm with bizarre, late occurring extrasystoles. (b) Lead V3 shows a short run of polymorphous ventricular tachycardia. (c) Recording (on lead V2) 24 hours after withdrawal of Sotazide shows QTc interval of 0.44 s. (d) Continuous ambulatory (Holter) recording at 2.5 mm/s shows the frequency of the short runs of ventricular tachycardia.

## Discussion

A polymorphous ventricular tachycardia was observed in 12 of our 13 patients. Features classical of torsade de pointes<sup>3, 18</sup> were identified in 10 of the 11 patients who had electrocardiographic recordings of the ventricular tachycardia. In all 11 patients the arrhythmia was initiated by a ventricular extrasystole occurring on the preceding T wave. In only one patient (case 10) was a ventricular tachycardia neither recorded nor observed on a monitor. Nevertheless it is highly likely that a ventricular tachyarrhythmia was responsible for her syncope since she had ventricular bigeminy with the R on T phenomenon and a notably prolonged QT interval. Furthermore, the syncope did not recur after withdrawal of the drugs.

In 1970 Singh and Vaughan Williams showed that sotalol (MJ1999) prolonged the repolarisation phase of the ventricular action potential in isolated cat papillary muscle and that it prolonged the QTc interval of the electrocardiogram in anaesthetised guinea pigs.<sup>10</sup> Several workers have shown that these class III antiarrhythmic effects also occur in man,<sup>9, 11, 19</sup> and this has raised the probability that sotalol has antiarrhythmic properties distinct from those of other beta blocking agents. Prolongation of the QTc interval may occur with sotalol in therapeutic doses,<sup>20-22</sup> and Neuvonen *et al* have reported a correlation between the serum sotalol concentration and prolongation of the QTc interval.<sup>20</sup> Although the implications of the prolonged QT interval induced by drugs such as sotalol have not yet been clarified, there appears to be an increased risk of ventricular tachycardia supervening.<sup>3</sup> The notably prolonged QTc intervals in our patients suggested that the ventricular arrhythmias were associated with the class III properties of sotalol. They were not, however, in accord with the relatively low daily dose of sotalol and were similar to those observed in patients with sotalol intoxication.<sup>15, 16</sup> We consider it probable that another factor was nearly always responsible for the electrophysiological environment in which sotalol became arrhythmogenic.

The importance of hypokalaemia as a cause of, or contributing factor to, the development of torsade de pointes has been emphasized,<sup>2, 7</sup> and in our view potassium depletion played a vital role in most, if not all, of our cases. In two recent reports of drug induced ventricular tachyarrhythmias, hypokalaemia was an associated feature in three of four cases reported by Ko *et al*<sup>7</sup> and in six of 11 cases reported by Khan *et al*.<sup>23</sup> Definite hypokalaemia was detected in eight of our 13 patients, although this was mild (serum potassium concentration 3-3.5 mmol/l) in five. Another three had serum potassium concentrations below 4 mmol/l, and thus only two patients (cases 3 and 12) had a serum potassium concentration above this value. Hypokalaemia

alone could not have been responsible for the ventricular arrhythmias because the QT intervals were very prolonged, a feature that certainly cannot be explained on that basis. None the less, hypokalaemia does appear to have been an important predisposing factor. In three of the eight patients (cases 4, 7, and 10) with definite hypokalaemia, there were additional factors which may have contributed to the prolonged QT interval and the ventricular extrasystoles. Two patients (cases 7 and 10) were taking disopyramide, a drug known to predispose to torsade de pointes.<sup>6, 7</sup> Disopyramide had been given concomitantly with Sotazide in one (case 7) of these two. The other patient (case 10) was also taking imipramine 50 mg daily, which is too small a dose to play a primary role but which may well have contributed to the prolonged QT interval.<sup>24</sup> The third patient (case 4) had been taking amitriptyline and imipramine for nine months. In all three patients syncope occurred within 48 hours of taking Sotazide.

Of the five patients (cases 1, 3, 5, 8, and 12) who did not have serum potassium concentrations below 3.5 mmol/l, there were four (cases 1, 3, 5, and 8) in whom no factor other than Sotazide could be implicated. One of these patients (case 3) had had a renal transplantation two days before taking Sotazide and probably had impaired renal excretion with resulting high serum concentrations of sotalol. In support of this is the fact that the QTc interval took three days to return to normal, although she had taken a total of only five tablets of Sotazide. The second patient (case 1) without definite hypokalaemia (serum potassium concentration 3.6 mmol/l) developed syncope within two hours of taking one tablet of Sotazide. Two others (cases 5 and 8) had serum potassium concentrations of 3.8 mmol/l after taking Sotazide for five weeks and one year. An arrhythmogenic role of a low myocardial potassium concentration in these latter three patients with normal, albeit relatively low, serum potassium concentrations cannot be excluded since the relation between myocardial potassium, total body potassium, and serum potassium concentrations remains uncertain.<sup>25</sup> The fifth patient (case 12) had a serum potassium concentration of 4.2 mmol/l which is the highest value in our series. She had been taking Sotazide two tablets daily for a year but had been given disopyramide 300 mg daily two weeks before her syncopal attack.

Sotalol, like amiodarone,<sup>26</sup> is reputedly a highly effective drug in the management of refractory, often life threatening, ventricular tachycardia.<sup>12</sup> It acts by prolonging the action potential duration of the ventricular muscle without altering the resting membrane potential, in effect delaying repolarisation. This delay is represented by prolongation of the QT interval, which probably reflects an overall increase in the

refractory period of cardiac muscle.<sup>27</sup> From the data currently available, some prolongation of the QT interval will occur in many patients taking sotalol.<sup>9 20-22</sup> The risk of their developing torsade de pointes is unknown and requires further investigation. There may be predisposing "sensitivity" factors that render sotalol particularly dangerous in individual patients but which require clarification. From our experience, we conclude that hypokalaemia, even when mild, is one such factor. Concomitant treatment with disopyramide is probably another, and high serum sotalol concentrations<sup>13 14</sup> are a third. The prescribing of sotalol, when other beta blockers are equally suitable, together with a thiazide diuretic constitutes an unjustifiable risk in the long term treatment of any condition—most notably hypertension—in which hypokalaemia commonly ensues as a consequence of the diuretic therapy. We, therefore, see little justification for the use of the combined preparation, Sotazide.

It is our present policy to confine the use of sotalol to those situations in which both its class III antiarrhythmic and beta receptor blocking effects are required. We have had favourable experience with the drug in the treatment of atrial and ventricular arrhythmias. Because of its class III property sotalol may be superior to other beta blockers in the long term therapy of hypertrophic cardiomyopathy and symptomatic primary mitral valve prolapse, but these observations require confirmation. Similarly, and despite the findings of Julian and co-workers that sotalol failed to reduce the incidence of sudden death as opposed to reinfarction during the first year after myocardial infarction,<sup>28</sup> this unique beta receptor blocking agent may still prove advantageous in treating selected cases of ischaemic heart disease. Under all circumstances, hypokalaemia must be avoided, and thus patients should be advised to stop taking sotalol should—for example—an attack of acute gastroenteritis develop. Sotalol should also be given extremely cautiously in conjunction with other drugs known to prolong the QT interval such as class I antiarrhythmic agents, phenothiazines, and tricyclic antidepressants.

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