

Electrophysiological effects of sotalol—just another beta blocker?

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SUMMARY The electrophysiological effects of intravenous sotalol hydrochloride (0.4 mg/kg) were assessed in 24 patients, including 13 with the Wolff-Parkinson-White syndrome, undergoing routine electrophysiological study. Fifteen to 30 minutes after sotalol administration there was a significant increase in sinus cycle length and in sinus node recovery time. There was a small increase in the AH interval, but the HV interval was unchanged. The QT and JT intervals, measured during sinus rhythm, were both increased. The atrial, ventricular, and atrioventricular nodal effective refractory periods were all prolonged, as was the atrioventricular nodal functional refractory period. In 13 patients with ventricular pre-excitation there was an increase of the accessory pathway anterograde and retrograde effective refractory periods. In 12 of these 13 sotalol was given during atrioventricular re-entrant tachycardia, resulting in termination in five. Tachycardia cycle length increased in all patients, with the major effect being in the atrioventricular direction. Though some of the effects seen in these patients are consistent with the beta adrenergic antagonist properties of sotalol, the effect on atrial, ventricular, and accessory pathway effective refractory periods and on ventricular repolarisation is not typical of that observed with other beta blockers but may be the result of lengthening of the action potential duration. These findings suggest that sotalol may be a more versatile antiarrhythmic agent than other beta receptor antagonists.

Sotalol hydrochloride was initially described as a pure beta adrenergic antagonist with class II antiarrhythmic action, but lacking cardioselectivity, intrinsic sympathomimetic effect, or local anaesthetic properties.¹⁻³ Subsequent animal investigations have shown that sotalol also causes a large increase in the action potential duration, similar to that seen with amiodarone.^{4,5} These observations have recently been supplemented by the findings of Edvardsson *et al.*⁶ who noted prolongation of right ventricular monophasic action potentials in man. These effects are consistent with class III action.³

A previous pilot study from our laboratory failed to show conclusively whether or not sotalol possesses class III antiarrhythmic activity.⁷ The present work was performed in order to clarify further the clinical cardiac electrophysiological effects of sotalol in a group of patients including those with the Wolff-Parkinson-White syndrome.

*Recipient of a British Heart Foundation Fellowship.

†Recipient of a grant from the Joint Research Board, St Bartholomew's Hospital.

Accepted for publication 16 February 1982

Patients and methods

Twenty-four consecutive patients, aged between 12 and 73 years, were investigated during routine electrophysiological study. Nineteen had complained of recurrent palpitation, three of dizzy spells, and two had suffered syncopal attacks. Thirteen patients (group A) had electrophysiological evidence of pre-excitation and were considered to have the Wolff-Parkinson-White syndrome. Atrioventricular re-entrant tachycardia had been documented in all 13. Eleven patients (group B) showed no evidence of pre-excitation and had a variety of electrophysiological diagnoses. Clinical and electrocardiographic details of all patients are shown in the Table.

Electrophysiological studies were performed as previously described.^{8,9} All patients gave informed consent and were studied in the non-sedated, post-absorptive state. Cardioactive medications were stopped for at least three drug elimination half-lives before study. High right atrial and His bundle electrograms were recorded in all patients. Distal and proximal

Table Patient details

Case No.	Age (y)	Sex	Symptoms	Electrocardiogram	Electrophysiological diagnosis
Group A					
1	23	F	Syncope	WPW B	Septal AP, AVRT
2	48	M	Palpitation	WPW A	Left-sided AP, AVRT
3	56	F	Palpitation	WPW A	Left-sided AP, AVRT
4	24	M	Palpitation	WPW A	Left-sided AP, AVRT
5	37	M	Palpitation	WPW A	Left-sided AP
6	22	F	Palpitation	WPW A	Left-sided AP, AVRT
7	51	M	Presyncope	WPW A	Left-sided AP, AVRT
8	32	M	Palpitation	WPW A	Left-sided AP, AVRT
9	13	F	Palpitation	WPW A	Left-sided AP, AVRT
10	73	M	Palpitation	WPW A	Left-sided AP, AVRT
11	12	F	Palpitation	WPW A	Left-sided AP, AVRT
12	23	F	Palpitation	WPW A	Left-sided AP, AVRT
13	50	F	Palpitation	WPW A	Left-sided AP, AVRT
Group B					
14	58	M	Palpitation	RBBB	Atrial tachycardia
15	60	F	Syncope	LBBB	Bundle branch disease
16	39	M	Palpitation	Normal	Atrial fibrillation
17	61	M	Palpitation	Normal	Dual AH, AVNRT
18	45	F	Palpitation	Normal	Dual AH, AVNRT
19	20	M	Presyncope	Long PR	Vagotonia
20	43	M	Palpitation	Short PR	Short AH
21	65	M	Presyncope	RBBB	Bundle branch disease
22	44	M	Palpitation	Short PR	Short AH
23	49	M	Palpitation	Ant. MI	Ventricular tachycardia
24	32	M	Palpitation	Normal	Normal

Ant. MI, anterior myocardial infarction; AP, accessory atrioventricular pathway; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; dual AH, functional duality of AH conduction; LBBB, left bundle-branch block; RBBB, right bundle-branch block; WPW, Wolff-Parkinson-White abnormality.

coronary sinus electrograms were recorded using a quadripolar electrode catheter in all group A patients and in several from group B. Stimulating electrodes were positioned in the high right atrium and right ventricular apex. Three or four surface electrocardiographic leads were recorded simultaneously. Recordings were made at a paper speed of 100 mm/s using a Mingograf ink pen recorder*, and stimulation was achieved with a Devices 4279 isolated stimulator†, emitting square wave pulses of 2 ms duration at approximately twice the diastolic threshold.

The following measurements were repeated using a similar technique 15 to 30 minutes after the infusion of sotalol (0.4 mg/kg) given over five minutes: sinus cycle length (averaged over 10 consecutive cycles); sinus node recovery time¹⁰ after high right atrial pacing for one minute at rates of 90, 120, and 150 beats per minute; PA,^{9,11} AH, and HV^{9,12,13} intervals; QT interval^{9,14}; QRS duration (measured from the earliest point of ventricular activation to the latest J point in any lead); atrial,^{9,15} ventricular,^{9,16} atrioventricular nodal,^{9,15} accessory pathway anterograde and retrograde^{9,17} effective refractory periods; atrioventricular nodal functional refractory period.^{9,15}

The corrected QT was calculated using Bazett's correction: $QT_c = QT / \sqrt{RR}$ in seconds.¹⁸ The JT

interval (QT-QRS) was calculated as a further index of ventricular repolarisation, relatively independent of changes in depolarisation.⁹ To minimise further the rate-related changes in the QRS duration and in the QT and JT intervals, these variables were also measured during atrial pacing at identical rates both before and after drug administration.

Refractory periods were measured using the extra-stimulus technique,¹³ at a constant driven pacing cycle length of 600 ms unless this exceeded the spontaneous sinus cycle length, when a slightly shorter cycle length was used.

Tachycardia cycle length was also measured (the mean atrial to atrial interval during tachycardia averaged over 10 consecutive beats), as were the tachycardia atrioventricular (intrinsicoid deflection of the low right atrial electrogram to the onset of the ventricular activation) and ventriculoatrial (onset of ventricular activation to the intrinsicoid deflection of the low right atrial electrogram) intervals. Where tachycardia was terminated by sotalol, the tachycardia intervals after sotalol were measured from the 10 beats immediately before reversion.

Statistical analyses were performed using Student's two tailed t test for paired data, except for the measurements of accessory pathway refractoriness, where the Wilcoxon sign rank test was used in order to include patients in whom initial accessory pathway refractory period measurements were limited by the

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refractoriness of the paced chamber or in whom sotalol caused complete conduction block.

Results

The dose of sotalol used varied from 18 to 32 (mean 24) mg. All measurements are written as the mean value \pm one standard deviation from the mean.

SINUS NODE FUNCTION

Sinus cycle length increased in all patients from 739 ± 107 to 869 ± 109 ms ($p < 0.001$). Sinus node recovery time, measured only in group B patients, increased from 1084 ± 302 to 1270 ± 301 ms ($p < 0.01$).

CONDUCTION

There was a small increase in the PA interval from 43 ± 13 to 45 ± 13 ms ($p < 0.02$), and a larger increase in the AH interval from 82 ± 28 to 94 ± 32 ms ($p < 0.001$). The AH interval could not be measured in one group A patient (case 1) because of the degree of pre-excitation. In the patients without pre-excitation (group B) there was no significant change in the HV interval (44 ± 12 to 45 ± 13 ms). In these patients there was no significant increase in the QRS duration measured during sinus rhythm (102 ± 20 to 106 ± 19 ms) or during constant rate atrial pacing (104 ± 19 to 106 ± 20 ms). The QT interval increased from 401 ± 45 to 427 ± 38 ms ($p < 0.01$) (Fig. 1a), and the paced QT interval from 388 ± 43 to 400 ± 37 ms ($p < 0.01$) (Fig. 1b), but the QTc was not significantly increased (450 ± 48 to 455 ± 46 ms) (Fig. 1a). The JT interval increased from 300 ± 44 to 321 ± 35 ms ($p < 0.02$) (Fig. 1a) and the paced JT interval from 284 ± 37 to 294 ± 31 ms ($p < 0.05$) (Fig. 1b).

REFRACTORINESS

The atrial effective refractory period increased from 216 ± 38 to 233 ± 40 ms ($p < 0.01$), and effective refractory period of the ventricle from 231 ± 30 to 242 ± 31 ms ($p < 0.01$). The effective refractory period of the atrioventricular node was limited by atrial refractoriness or obscured by accessory pathway conduction in 12 patients. In the remaining 12 there was an increase from 294 ± 87 to 338 ± 90 ms ($p < 0.001$). The functional refractory period of the atrioventricular node was limited by atrial refractoriness in 11 patients and in the remaining 13 increased from 417 ± 92 to 467 ± 86 ms ($p < 0.001$). The effective refractory period of accessory pathway in the anterograde direction was limited by atrial refractoriness in three patients, increased in eight, decreased in one, and remained unchanged in the other, an overall increase from 317 ± 88 to 350 ± 81 ms ($p < 0.02$). The effective refractory period of the accessory pathway in the retrograde direction was limited by ventricular refrac-

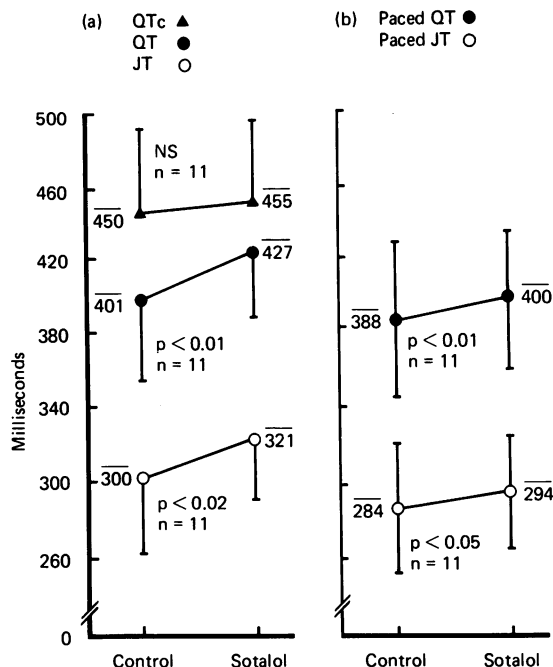


Fig. 1 The effect of sotalol on indices of ventricular repolarisation. The QT, QTc, and JT intervals are shown in panel (a); the QT and JT intervals during constant rate atrial pacing are shown in panel (b).

toriness in three patients. In the other 10 patients, complete accessory pathway block occurred in two (effective refractory period of the accessory pathway in the retrograde direction > 600 ms), refractoriness increased in six and decreased in two, an overall change from 296 ± 40 to 371 ± 139 ms ($p < 0.05$).

TACHYCARDIA INTERVALS

Sotalol was given during tachycardia in 12 out of the 13 group A patients, terminating it in five. An example of anterograde termination is shown (Fig. 2). The mean total cycle length increased from 355 ± 64 to 413 ± 54 ms ($p < 0.001$) (Fig. 3a). This increase occurred predominantly in the atrioventricular direction, the tachycardia atrioventricular interval increasing from 230 ± 69 to 286 ± 54 ms ($p < 0.001$), with only a small increase in the tachycardia ventriculoatrial interval from 125 ± 25 to 132 ± 25 ms ($p < 0.01$) (Fig. 3b).

Discussion

In 1965 Lish *et al.*¹ showed that sotalol, in common with other beta antagonists, prevented isoprenaline-induced tachycardia. Since then numerous reports have shown that sotalol is moderately effective for the

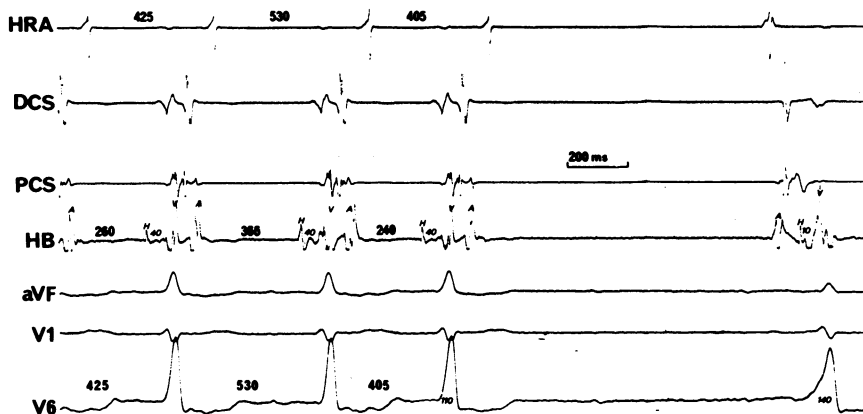


Fig. 2 Electrographic recording of anterograde termination of an atrioventricular re-entrant tachycardia by sotalol in a patient with the Wolff-Parkinson-White syndrome. Note the alternation of cycle length before reversion occurs. High right atrial (HRA), distal coronary sinus (DCS), proximal coronary sinus (PCS), and His bundle (HB) electrograms are shown, together with three standard surface leads (aVF, V1, V6). V=ventricular electrogram, A=atrial electrogram. The paper speed is 100 mm/s.

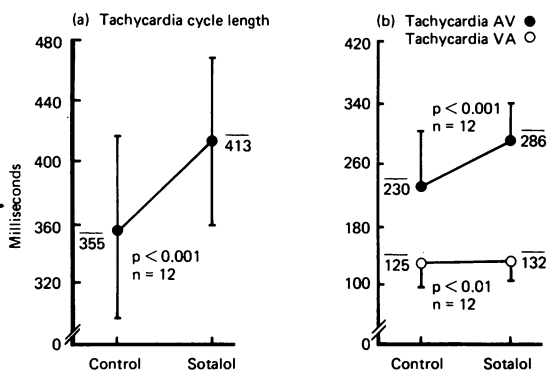


Fig. 3 The effect of sotalol on tachycardia cycle length and on the tachycardia atrioventricular (AV) and ventriculoatrial (VA) intervals.

treatment and prevention of a wide spectrum of arrhythmias.¹⁹⁻²¹ Several beta receptor antagonists have been investigated during cardiac electrophysiological study²²⁻²⁴ and, like sotalol, most prolong sinus cycle length and the sinus node recovery time²⁵ as well as increasing atrioventricular nodal conduction time (AH interval) and atrioventricular nodal refractoriness. Sotalol, in common with pindolol²⁶ and atenolol,²⁷ has also been shown to increase atrial refractoriness.

Although the antiarrhythmic properties of sotalol have previously been ascribed to beta receptor antagonism alone,^{28,29} Singh and Vaughan Williams⁴ reported that sotalol caused prolongation of atrial and ventricular action potentials in isolated rabbit and cat myocardium. It also increased the QTc interval in

anaesthetised guinea-pigs, but had negligible local anaesthetic (membrane stabilising) effects. From these studies it was concluded that sotalol has class III antiarrhythmic activity in addition to beta receptor antagonism.

Ward *et al.*⁷ have previously reported a limited clinical study showing that sotalol (0.4 mg/kg) causes a significant increase in sinus cycle length, sinus node recovery time, the AH interval, the atrial effective refractory period, and the effective and functional refractory periods of the atrioventricular node, but a statistically insignificant increase in the effective refractory period of the ventricle. None of the patients studied had an atrioventricular accessory pathway, and indices of repolarisation such as the QT and JT intervals were not examined. Edvardsson *et al.*⁶ using a higher dose of sotalol (100 mg in seven of eight patients), found a significant increase in both the effective refractory period of the ventricle (248 ± 24 to 276 ± 21 ms ($p < 0.001$)), and in monophasic action potentials measured using special suction electrodes positioned in the right ventricular apex (248 ± 18 to 290 ± 29 ms ($p < 0.01$)). Echt *et al.*³⁰ recently reported that sotalol, and not propranolol, prolonged atrial and ventricular refractory periods, and also the monophasic action potentials. Both groups agreed with Singh and Vaughan Williams⁴ that sotalol differed significantly from other beta antagonists. The present study has confirmed that sotalol causes a moderate prolongation of the atrial and the ventricular effective refractory periods. Accessory pathway refractoriness also increased in both the anterograde and retrograde direction, an effect that has not been noted with other beta antagonists.³¹

In this study, and that briefly reported by Echt and colleagues,³⁰ sotalol significantly prolonged the QT interval measured during sinus rhythm. The QT interval assessed during identical rate atrial pacing was also increased by sotalol, but this has not been the case with propranolol.³² The prolongation of the QT was confined to the JT interval as the QRS complex width did not prolong. In the present study the QTc lengthened very slightly but this change was not significant. Bazett's correction of the QT interval (QTc) was formulated to allow for physiological variation in heart rate, and is of uncertain value in pharmacological studies. Neuvonen *et al.*,³³ however, have demonstrated an approximately linear relation between QTc prolongation and serum sotalol concentration. In addition, a number of investigators have shown dramatic increases of the QT and QTc intervals associated with sotalol intoxication and in several instances this has been associated with ventricular arrhythmias (torsade de pointes).³⁴⁻³⁶

The effects of sotalol on the ventricular and accessory pathway effective refractory periods and on the QT and JT intervals are not typical of beta adrenergic antagonists, but are seen with other drugs which prolong the action potential and are consistent with additional class III action. Similar electrophysiological and proarrhythmic effects have been found with the prototype class III agent, amiodarone.³⁷⁻³⁹

The efficacy of sotalol, however, when given during established atrioventricular re-entrant tachycardia in this study is disappointing. Though tachycardia slowed in all patients it terminated in only five, with termination occurring in the anterograde direction. Furthermore, the tachycardia atrioventricular interval prolonged to a greater extent than the ventriculoatrial interval, suggesting a predominantly atrioventricular nodal effect.

Sotalol shows the electrophysiological effects of a class III antiarrhythmic agent as well as those of a competitive beta receptor antagonist, but the relevance of these findings to clinical practice requires further evaluation.

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