Acute prolongation of myocardial refractoriness by sotalol

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SUMMARY Sotalol, a beta adrenoceptor antagonist, was given intravenously to 15 patients with accessory atrioventricular pathways during intracardiac electrophysiological studies. Eleven patients had the Wolff-Parkinson-White syndrome and four patients had concealed left sided accessory pathways. Four patients were restudied while receiving oral sotalol.

In contrast to the actions typical of beta blocking agents, intravenous sotalol prolonged the effective refractory periods of the ventricles and accessory pathways and reduced the ventricular response to atrial fibrillation in the patients with the Wolff-Parkinson-White syndrome. Similar results were obtained with oral administration.

These findings support the observation that sotalol, unlike other beta blocking agents, causes acute prolongation of the myocardial action potential and suggest that this action might be of therapeutic use.

In 1970 Singh and Vaughan Williams¹ showed in vitro that sotalol, unlike other beta adrenoceptor antagonists, prolonged the action potential of the myocardial cell. This effect, designated "class III" in their classification of antiarrhythmic actions, is also possessed by amiodarone,^{2,3} raising the possibility that sotalol might have important antiarrhythmic actions not associated with other beta blocking agents.

Only recently has it been shown that sotalol prolongs the myocardial action potential duration in man: in eight patients with chronic atrial fibrillation the drug given intravenously in a dose of 40 to 100 mg prolonged ventricular repolarisation by 13 to 17%.⁴ Ward *et al.*,⁵ however, using a smaller dose of 0.4 mg per kg body weight were unable to show significant prolongation of the ventricular effective refractory period and concluded that sotalol only had electrophysiological actions typical of all beta blockers, that is depression of sinus node automaticity and atrioventricular nodal conduction.⁶

In this study patients with an accessory atrioventricular pathway either overt (that is Wolff-Parkinson-White syndrome) or concealed^{7,8} were selected for study because they provided two indices, ventricular and accessory pathway refractoriness, which should be affected by a class III drug but not by beta adrenoceptor blockade^{5,7,9} (myocardial refractor-

iness may also be prolonged by membrane stabilising drugs⁷ but sotalol does not have this property¹). In the patients with Wolff-Parkinson-White syndrome the effect of sotalol on a third variable, the ventricular response to atrial fibrillation, was also assessed. In the Wolff-Parkinson-White syndrome, atrial fibrillation cannot usually be controlled by drugs which depress atrioventricular nodal conduction because in most cases the majority of atrial impulses are conducted to the ventricles via the accessory pathway.⁷ The ventricular response can be very rapid and may thereby cause ventricular fibrillation; most episodes of ventricular fibrillation occur in patients in whom the shortest interval between pre-excited ventricular complexes during atrial fibrillation is less than 205 ms.⁷ Measurement of this interval has been used to assess the effect of drugs on the accessory pathway^{10,11} and provides the opportunity to see whether sotalol, like amiodarone,¹² can be effective in controlling an arrhythmia which will not respond to beta adrenoceptor blockade.^{7,9}

Patients and methods

Fifteen patients prone to paroxysmal tachycardia, aged 19 to 63 years, were studied. Eleven had the Wolff-Parkinson-White syndrome (five type A and six type B) and four had concealed left sided accessory atrioventricular pathways. Diagnoses were based on

standard electrophysiological criteria^{7,8} and informed consent was obtained. Antiarrhythmic drugs were stopped at least 72 hours before study and, in two patients who had failed to respond to amiodarone, therapy was discontinued three months beforehand.

Electrograms from the lateral right atrium, septal region of the right atrium, bundle of His, and left atrium were recorded simultaneously via transvenous electrodes which were introduced into the right femoral and a left antecubital vein under local anaesthesia and advanced to the right atrium, tricuspid valve region, right ventricular apex, and coronary sinus, respectively.¹³ Surface leads I, II, and VI were also recorded. Recordings were made by means of a six channel electrocardiograph recorder at a paper speed of 100 mm/s.

The effective refractory periods of the atria, ventricles, and accessory pathway were measured by the extrastimulus technique¹³ using a programmable stimulator. Atrial and ventricular effective refractory periods were defined as the longest coupling intervals of atrial or ventricular extrastimuli which did not result in atrial or ventricular depolarisation, respectively. The effective refractory period of the accessory atrioventricular pathway in the anterograde direction was defined as the longest coupling interval of an atrial extrastimulus which resulted in atrial activation but failure of conduction over the accessory pathway and hence loss of delta wave. The effective refractory period of the accessory pathway in the retrograde direction was defined as the longest coupling interval of a ventricular extrastimulus which failed to be conducted to the atria by the accessory pathway as judged from absence of eccentric atrial activation and/or abrupt increase in ventriculoatrial conduction time.

Where possible, atrioventricular re-entrant tachycardia was initiated and terminated by precisely timed premature atrial or ventricular stimuli.¹³ In the patients with Wolff-Parkinson-White syndrome, atrial fibrillation was initiated by rapid atrial pacing.⁷

Measurements were repeated 10 to 20 minutes after the completion of an infusion of sotalol hydrochloride, 1.5 mg per kg body weight, given over five

minutes. This dose was used because it is in the same order of magnitude as the recommended oral dosage (the bioavailability of sotalol is almost 100%¹⁴). Four patients were restudied after an interval of two days, three weeks, 10 weeks, or 12 weeks after treatment with oral sotalol had been started (160 mg twice daily).

Results

INTRAVENOUS SOTALOL

The drug did not cause any unwanted effects.

The effective refractory periods of the atria, ventricles, and accessory pathways were prolonged by sotalol and both the cycle length during atrioventricular re-entrant tachycardia and the minimum interval between pre-excited beats during atrial fibrillation were increased. In three patients sotalol was given during atrial fibrillation. The ventricular rate slowed two minutes after the injection but sinus rhythm did not return for six, 12, and 18 minutes, respectively. The results from patients where measurements could be made both before and after intravenous sotalol are summarised in the Table and in Fig. 1-6.

It was not possible to obtain complete data in all patients. In seven patients, atrial refractoriness exceeded refractoriness of the accessory pathway in the anterograde direction, preventing measurement of the latter. Similarly, in three patients measurement of the effective refractory period of the accessory pathway in the retrograde direction was not possible because it was less than the ventricular effective refractory period. In three patients, premature atrial stimulation initiated atrial fibrillation, preventing measurement of the atrial effective refractory period. Atrial fibrillation persisted in two patients, preventing measurement of the effective refractory periods of the ventricles and accessory pathway. Atrial refractoriness was not measured in two patients because atrial stimulation repeatedly induced atrioventricular re-entrant tachycardia. Atrioventricular re-entrant tachycardia could not be initiated in five patients

Table Mean values and standard deviations of effective refractory periods, cycle lengths during AV re-entrant tachycardia (AVRT) and minimum interval between pre-excited ventricular complexes during atrial fibrillation (RR_{min}) in milliseconds before and after intravenous sotalol

	Effective refractory periods				AVRT	RR_{min}
	Atria	Ventricles	AP_{AV}	AP_{VA}		
Before	224 ± 37	209 ± 23	297 ± 75	295 ± 50	372 ± 68	268 ± 77
After	264 ± 49	245 ± 20	360 ± 75	349 ± 65	423 ± 64	351 ± 63
No.	10	13	3	11	6	11
p	<0.002	<0.002	<0.01	<0.002	<0.05	<0.002

No., number of patients with data before and after sotalol; p, significance level determined by Wilcoxon's signed ranks test; AP_{AV} and AP_{VA} , refractory periods of accessory pathway in anterograde and retrograde directions, respectively.

Fig. 1 Atrial effective refractory periods before (pre), after intravenous (iv) and oral sotalol.

before or after sotalol and in a further four patients after sotalol had been given.

ORAL SOTALOL

Electrophysiological measurements after oral sotalol were similar to those after intravenous administration (Fig. 1-6). Atrial fibrillation occurred in two patients, preventing measurement of atrial refractoriness in both, and anterograde accessory pathway refractoriness in one. In two patients, atrial refractoriness exceeded that of the accessory pathway in the antero-

Fig. 2 Ventricular effective refractory periods before (pre), after intravenous (iv) and oral sotalol.

grade direction, precluding measurement of the latter. In one patient ventriculoatrial conduction was blocked by oral sotalol. Technical difficulties in recording an atrial electrogram during ventricular pacing prevented measurement of retrograde accessory pathway refractoriness in one patient.

Discussion

This study shows that, in contrast to other beta blocking drugs,⁵⁻⁹ sotalol acutely prolongs ventricular and accessory atrioventricular pathway refractoriness, thereby supporting the *in vitro*¹ and *in vivo*⁴ observations that sotalol, in addition to being a beta adrenoceptor antagonist, prolongs the duration of the myocardial action potential. Atrial refractoriness was also prolonged but this action is not unique to sotalol: atenolol¹⁵ and pindolol¹⁶ also prolong the atrial effective refractory period though the mechanism is not clear.⁵

That sotalol has electrophysiological actions in

Fig. 3

Fig. 5

Fig. 4

Fig. 3 Effective refractory periods of the accessory pathway in the anterograde direction in three of the patients with Wolff-Parkinson-White syndrome before (pre) and after intravenous (iv) sotalol.

Fig. 4 Effective refractory periods of the accessory pathway in the retrograde direction before (pre), after intravenous (iv) and oral sotalol.

Fig. 5 Cycle length during atrioventricular re-entrant tachycardia before (pre), after intravenous (iv) and oral sotalol. An asterisk indicates that sotalol prevented initiation of tachycardia.

Fig. 6 Minimum interval between pre-excited ventricular complexes during atrial fibrillation in patients with Wolff-Parkinson-White syndrome before (pre), after intravenous (iv) and oral sotalol.

common with amiodarone suggests that it might have important antiarrhythmic properties other than those resulting from beta adrenoceptor blockade. A large trial comparing the clinical antiarrhythmic effects of sotalol with another beta blocking agent is required to answer this question. The reduction of ventricular rate during atrial fibrillation in the patients with Wolff-Parkinson-White syndrome with both intravenous and oral sotalol does, however, demonstrate that the drug can be effective in the treatment of an arrhythmia which will not respond to beta adrenoceptor blockade.⁷ Furthermore, prolongation by sotalol of refractoriness of the accessory pathway, which forms the retrograde limb in many atrioventricular re-entrant tachycardias,⁷ may be useful in the prophylaxis of this arrhythmia.

Recently, metoprolol has been shown to prolong myocardial action potential duration in man after chronic, but not acute, administration.¹⁷ The same phenomenon has been shown in rabbits with several

beta blocking drugs.¹⁸ Even though chronic beta blockade may confer a class III effect it does not, however, lead to the same impressive antiarrhythmic efficacy as amiodarone.³ Either the efficacy of amiodarone results from actions other than its class III effect or, more probably, there are quantitative differences between the class III actions of chronic beta blockade and amiodarone.

One mechanism by which amiodarone is thought to be effective is by uniformly prolonging action potential duration throughout the myocardium and thereby reducing the heterogeneity of action potential duration which can predispose to ventricular arrhythmias.¹⁹ Sotalol may well have a similar action but it should be noted that there have been a number of reports of ventricular arrhythmias being caused by extremely high doses of sotalol.²⁰

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