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Cellular electrophysiological effects of D- and DL-sotalol in guinea-pig sinoatrial node, atrium and ventricle and human atrium: differential tissue sensitivity

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1 The effects of racemic DL-sotalol and D-sotalol on guinea-pig sino-atrial node, atrium and ventricle and on human atrium were studied using standard microelectrode techniques. Both compounds increased spontaneous sinus node cycle length largely by prolonging the repolarization phase of the action potentials. This effect was attributed to blockade of outward potassium current.

2 Ventricular action potential duration was similarly prolonged by DL-sotalol at concentrations of 5–50 μM.

3 DL-Sotalol 1–50 μM had no effect on guinea-pig atrial action potential duration and D-sotalol produced minor prolongation only at the highest concentration (50 μM).

4 Human atrial action potentials were, however, significantly prolonged by both DL- and D-sotalol 10 μM. This indicates differential sensitivities to sotalol for human and guinea-pig atrium and explains the ability of sotalol to prolong atrial monophasic action potential duration in clinical studies.

Introduction

Sotalol is a non-selective β-adrenoceptor blocking agent which also significantly prolongs cardiac action potential duration (class III antiarrhythmic effect (Singh & Vaughan Williams, 1970)). It has been widely reported to be effective in the treatment of ventricular and supraventricular tachycardias (including those involving accessory atrio-ventricular connections) (Nathan *et al.*, 1982; Bennett, 1982). It is also of value in the reversion of acute atrial fibrillation (Campbell *et al.*, 1985). There remain, however, a number of unanswered questions concerning the nature of the antiarrhythmic properties of sotalol.

Firstly, there is considerable doubt as to whether these are due mostly or entirely to β-adrenoceptor blockade or to the class III action of the drug. There is evidence (mainly from measurements of QT interval changes on the electrocardiogram) that sotalol produces β-adrenoceptor blockade and antiarrhythmic effects at concentrations considerably lower than those at which class III effects are readily apparent (Campbell *et al.*, 1985; Neuvonen *et al.*, 1981).

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Of particular interest in this regard is the fact that *in vitro* studies of the electrophysiological effects of sotalol on animal cardiac action potentials have shown class III action on atrial cells only in concentrations far in excess of those seen in plasma during therapeutic use. Class III effects can, on the other hand, be demonstrated in these studies for ventricular and Purkinje fibres at clinically relevant concentrations (Singh & Vaughan Williams, 1970; Strauss *et al.*, 1970). In apparent contradiction to these findings, there is now convincing evidence of prolongation of both atrial and ventricular action potentials in man at therapeutic plasma sotalol concentrations (Edvardsson *et al.*, 1980; Hayward & Taggart, 1986), suggesting the possibility of species differences in terms of atrial sensitivity to sotalol.

Another approach to improving our understanding of the mechanism of the antiarrhythmic effects of sotalol has been afforded by the advent of D-sotalol. Unlike racemic (DL-) sotalol, the dextro isomer has virtually no β-adrenoceptor blocking activity (Somani & Watson, 1968; Lish *et al.*, 1969). However, it does possess class III properties and, in preliminary clinical studies, appears to have comparable antiarrhythmic

effects to DL-sotalol (Lynch *et al.*, 1984; Rowland *et al.*, 1985).

Finally, DL-sotalol is associated with sinus bradycardia in clinical use (Touboul *et al.*, 1984) and symptomatic sinus node depression has been reported (Senges *et al.*, 1984; Campbell *et al.*, 1985). This, of course, might be expected of a β-adrenoceptor blocking agent, but it is of great interest to note that some preliminary clinical studies have shown sinus node slowing with D-sotalol also (Rowland *et al.*, 1985).

The present study therefore was performed with three aims: firstly to document the cellular electrophysiological effects of racemic sotalol on atrial, ventricular and sino-atrial node cells from the same species (guinea-pig); secondly to compare these actions (particularly those on the sinus node) with those of D-sotalol; and finally to repeat the atrial cell studies using samples taken from human right atrial appendage in patients undergoing open-heart surgery for coronary artery disease. This last section of the study was designed to detect any difference in sensitivity to the class III effects of sotalol between human and guinea-pig atrial muscle.

Methods

Guinea-pigs of either sex weighing 500–800 g were killed by cervical dislocation and their hearts quickly removed. Studies on ventricular myocardium were performed on strips cut from the free wall of the right ventricle and pinned to the base of a tissue bath (volume 0.5 ml) with the endocardial surface uppermost. Atrial studies were performed on trabeculae taken from the left atrium and pinned in the same manner. The sinus node preparation consisted of a segment of the posterior wall of the right atrium, the borders of which were formed by the crista terminalis, the superior vena cava, the interatrial septum and the inferior vena cava. The tissue was superfused at 3 ml min^{-1} with modified Locke solution gassed with 95% O_2 and 5% CO_2 and maintained at 32 ± 0.2°C by a Peltier element. The composition of the Locke solution was as follows (mM): NaCl 125, KCl 5.6, $CaCl_2$ 2.16, $NaHCO_3$ 25, $MgCl_2$ 1.0, NaH_2PO_4 0.44, glucose 11 and the pH was 7.4.

Throughout the experiments the atrial and ventricular preparations were driven at a cycle length of 1000 ms by square waves (1 ms duration, twice threshold) delivered by a bipolar platinum electrode. The sinus node tissue was allowed to beat spontaneously. Action potentials were recorded with conventional glass microelectrodes filled with 3 M KCl (impedance 10–30 MΩ) and coupled to a high input impedance d.c. amplifier (Neurolog 102G). Preparations were allowed to equilibrate for 2–3 h before taking control recordings. Cumulative doses of sotalol were then added to the superfusate and new readings taken after exposure times of 30–60 min. In the case of the sinus node preparations, the equilibration period was used to explore the area adjacent to the crista terminalis to locate and obtain a stable impalement in a typical sino-atrial node cell (maximum diastolic potential less than −70 mV, marked spontaneous diastolic depolarization, followed by a smooth transition into a slow upstroke with a maximum rate of depolarization less than 10 Vs^{-1}). Experiments were commenced only after impalement of such a cell had been maintained for at least 15 min. Each experiment described with this preparation was performed during continuous recording from the same cell.

Human atrial tissue

Small samples of the right atrial appendage were obtained from 5 patients (3 men, 2 women aged 42–70 years) undergoing coronary artery bypass grafting. This piece of tissue, removed at the time of insertion of a large-bore cannula to take the venous return to the heart-lung machine, is normally discarded. It was collected in ice-cold 'cardioplegic' Locke solution (see below) and transported quickly to the laboratory where a small trabeculum (approximately 3 mm long and 1 mm in diameter) was removed and pinned to the same bath described above. It was then treated as described above for guinea-pig atrial preparations except that bath temperature was 37 ± 0.2°C. The composition of the cardioplegic solution was identical to standard Locke solution except that the levels of KCl and $MgCl_2$ were increased to 20 mM and 16 mM, respectively.

Analysis of recordings

The action potential was monitored on a storage oscilloscope. Analysis of specific recordings was performed by digital techniques using a Rockwell AIM-65 8-bit microcomputer modified by the addition of sampling hardware comprising a gain-matching amplifier, a sample-and-hold circuit and an Analog Devices ADC 571 10-bit analog-to-digital converter connected to two ports of the AIM-65 Versatile Interface Adaptor.

Atrial and ventricular potentials A machine language program, called from BASIC acquires up to 128 consecutive action potentials at three sampling rates (20 kHz for upstroke data, 1 kHz for the resting potential and 500 Hz for action potential duration). The following parameters were derived: resting potential, amplitude, maximum rate of depolarization (by simple differencing of 10-bit data samples), action potential duration to 50% and 90% repolarization (APD_{50}, APD_{90}).

Table 1 Effects of cumulative concentrations of DL-sotalol on ventricular action potentials

		DL-Sotalol				
	Control	*1 μM*	*5 μM*	*10 μM*	*50 μM*	*Wash-off*
APA (mV)	110.4 ± 4.1	109.3 ± 5.6	105.9 ± 8.0	108.7 ± 8.4	107.4 ± 6.2	110.4 ± 3.2
RP (mV)	−77.1 ± 3.8	−78.2 ± 4.9	−76.9 ± 4.5	−79.1 ± 3.8	−77.2 ± 3.7	−77.9 ± 4.5
V_{max} (Vs^{-1})	194.4 ± 54.6	210.4 ± 47.6	205.5 ± 41.5	210.3 ± 58.3	189.9 ± 46.6	214.7 ± 59.9
APD_{50} (ms)	153.4 ± 8.0	159.9 ± 10.0	170.3 ± 4.3†	185.8 ± 7.9†	215.7 ± 5.9†	205.7 ± 4.6†
APD_{90} (ms)	199.6 ± 15.1	207.4 ± 17.8	218.5 ± 14.0**	228.9 ± 7.5†	262.4 ± 8.8†	247.1 ± 5.2†

Exposure times = 60 min; $n = 15$. APA = action potential amplitude; APD_{50} and APD_{90} = action potential duration to 50% or 90% repolarization; RP = resting membrane potential; V_{max} = maximum rate of depolarization. $^{**}P < 0.01$; †$P < 0.0001$ (significance of difference from controls).

Sinus node potentials On command, a machine code program acquires 1000, 10-bit samples of the action potential at a rate of 1 kHz and saves them in memory. A BASIC program initiates the machine language program; waits for data acquisition and then takes the raw amplitude samples from memory for subsequent analysis during which the following parameters were estimated; peak (or overshoot) potential, maximum diastolic potential, action potential amplitude, take-off potential (transition between phase 4 and the upstroke of the next action potential), duration and slope of phase 4 depolarization, cycle length and the maximum slopes of phase 0 depolarization and of repolarization.

Drugs, (DL-sotalol and D-sotalol) were kindly supplied by Bristol-Myers, Australia. Data are expressed as means ± s.d. and significance of differences between means was assessed by Student's *t* test for paired or unpaired samples, as appropriate.

Results

Guinea-pig atrial action potentials

Exposure to DL-sotalol in concentrations of 5, 10 and 50 μM for up to 2 h had no effect on any of the action potential parameters measured ($n = 15$).

D-Sotalol also had no effect on atrial action potential in concentrations of 5 or 10 μM. Exposure to D-sotalol, 50 μM for 90 min, produced minor, reversible prolongation of APD_{50} and APD_{90} (43.4 ± 6.3 ms to 50.8 ± 9.4 ms, $P < 0.01$, and 126.1 ± 10.9 ms to 135.8 ± 9.7 ms, $P < 0.01$, respectively, $n = 5$.) No other parameters were changed significantly.

Ventricular potentials

DL-Sotalol produced a dose-dependent prolongation of both APD_{50} and APD_{90} at 5, 10 and 50 μM but no significant effect at 1 μM. This 'class III' effect reversed only slightly after 60 min washing in control solution (Table 1). No effects were seen on other parameters.

Two series of experiments were performed to study the effects of D-sotalol on right ventricular action potentials. The results of the first are summarized in Table 2. Large, highly significant increases in APD_{50} and APD_{90} were seen at concentrations of 5, 10 and 50 μM. In view of this finding a separate series of experiments was performed with this preparation in the presence of 1 μM D-sotalol. APD_{50} was prolonged from 151.5 ± 10.4 ms to 163.1 ± 14.5 ms ($P < 0.001$, $n = 30$) and APD_{90} from 195.7 ± 11.5 to

Table 2 Effects of cumulative concentration of D-solatol on ventricular action potentials

		D-Sotalol			
	Control	*5 μM*	*10 μM*	*50 μM*	*Wash-off*
APA (mV)	107.5 ± 6.3	107.8 ± 6.1	108.9 ± 4.3	106.7 ± 5.4	111.3 ± 5.5
RP (mV)	−76.2 ± 3.1	−77.9 ± 4.7	−78.6 ± 2.9	−77.1 ± 3.7	−77.0 ± 5.0
V_{max} (Vs^{-1})	237.7 ± 47.2	211.5 ± 54.9	209.9 ± 31.9	227.6 ± 33.1	255.0 ± 47.4
APD_{50} (ms)	140.1 ± 10.2	181.3 ± 15.4†	189.8 ± 11.7†	217.3 ± 16.5†	209.5 ± 29.0†
APD_{90} (ms)	178.1 ± 15.2	213.6 ± 12.5†	224.9 ± 10.6†	250.4 ± 12.1†	246.5 ± 19.6†

Exposure times = 60 min; $n = 15$. For abbreviations and symbols see Table 1.

208.0 ± 18.9 ms ($P < 0.01$, $n = 30$). Once again, D-sotalol had no significant effect on any other characteristics of the action potentials.

Sinus node potentials

The effects of DL-sotalol on sinus node action potentials were studied at concentrations of 5, 10 and 50 μM. Spontaneous cycle length was reversibly prolonged in a dose-dependent manner at all three concentrations (311.6 ± 17.9 to 323.8 ± 17.4 ms at 5 μM; $P < 0.05$; 330 ± 17.6 ms at 10 μM; $P < 0.01$; and 383.4 ± 28.8 ms at 50 μM; $P < 0.01$; $n = 5$). In each case, this effect on cycle length was apparent within 10 min of drug exposure and maximal within 30 min. Slowing of the rate of repolarization with consequent action potential prolongation accounted for virtually all the reduction in spontaneous rate (Figure 1). This effect was statistically significant at all three concentrations. At 50 μM only, there was, in addition, a significant depression of the rate of spontaneous diastolic depolarization (reduction of phase 4 slope). Details of the effects on various action potential parameters at 50 μM are given in Table 3. Take-off potential was not changed significantly.

The actions of D-sotalol 5, 10 and 50 μM were qualitatively identical to those of DL-sotalol except that the depression of phase 4 slope did not achieve statistical significance at any concentration studied (Table 3). The cycle length prolongations seen at the lower doses were 382 ± 12 to 396 ± 22 ms (not significant) at 5 μM, and to 405 ± 17 ms at 10 μM ($P < 0.01$). Once again the increases were due to prolongation of repolarization.

Human atrial action potentials

In five preparations both DL-sotalol and D-sotalol, 5 μM and 10 μM, consistently and reversibly prolonged

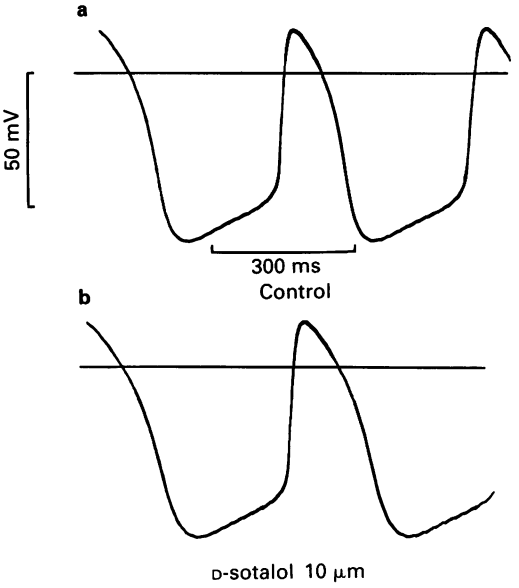

Figure 1 Action potentials recorded from the same guinea-pig sino-atrial node cell before (a) and after (b) 30 min exposure to D-solatol 10 μM. The spontaneous cycle length is prolonged and this effect is almost entirely due to slowing of repolarization. Virtually identical effects were seen with DL-sotalol.

APD_{90} without significant effects on other parameters (APD_{50} was not significantly affected). For DL-sotalol 10 μM, APD_{90} increased from a control value of 358 ± 54 ms (38 cells studied) to 389 ± 52 ms (33 cells studied; $P < 0.05$). For D-sotalol, 10 μM, these figures were 328 ± 57 ms (17 cells) and 361 ± 46 ms (24 cells; $P < 0.05$) respectively. Figure 2 illustrates these effects in one preparation which was exposed to both compounds in turn.

Table 3 Effects of 50 μM DL-sotalol and 50 μM D-sotalol on sinus node potentials

		DL-sotalol			*D-sotalol*	
	Control	*50 μM*	*60 min wash-off*	*Control*	*50 μM*	*60 min wash*
Cycle length (ms)	312 ± 18	383 ± 29**	309 ± 27	382 ± 12	427 ± 21**	387 ± 21
MDP (mV)	−64.2 ± 2.8	−63.1 ± 2.5	−63.6 ± 2.3	−65.7 ± 4.1	−65.6 ± 5.3	−65.9 ± 4.6
Amplitude (mV)	77.3 ± 9.0	75.8 ± 6.8	76.5 ± 5.9	79.1 ± 8.6	79.4 ± 11.0	80.1 ± 10.1
V_{max} (Vs^{-1})	4.0 ± 2.9	3.2 ± 1.7	3.8 ± 2.5	3.5 ± 1.4	3.0 ± 1.6	3.1 ± 1.3
Repolarization rate (Vs^{-1})	−0.97 ± 0.09	−0.60 ± 0.06†	−0.94 ± 0.10	−1.09 ± 0.2	−0.72 ± 0.21**	−1.02 ± 0.18
Phase 4 slope (mV^{-1})	148 ± 35	105 ± 22*	134 ± 30	139 ± 30	127 ± 34	139 ± 31
APD (ms)	199 ± 9	269 ± 21	203 ± 20	201 ± 12	247 ± 23	208 ± 6

Exposure times = 30 min; $n = 5$. *$P < 0.05$; **$P < 0.01$; †$P < 0.001$; significance of difference from controls. MDP = maximum diastolic potential; V_{max} = maximum rate of depolarization; APD = action potential duration.

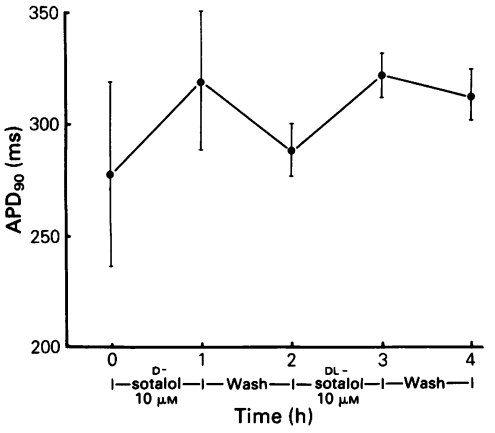

Figure 2 Effects on action potential duration (APD_{90}) of a single human atrial preparation of serial exposure to DL-sotalol and D-sotalol. Each point represents the mean of 8–12 cells and vertical lines show s.d.

Discussion

Effects on guinea-pig atrial and ventricular cells

Both D- and DL-sotalol produced dose-dependent prolongation of guinea-pig ventricular action potential duration without significant effects on other parameters measured (class III effect). In addition, D-sotalol, which possesses no significant β-adrenoceptor blocking properties, appeared to be at least as potent as DL-sotalol and perhaps more potent. D-Sotalol significantly prolonged APD_{50} and APD_{90} in concentrations of 1, 5, 10 and 50 μM and above. These data indicate that the class III actions of sotalol are an intrinsic property of the drug and not the result of its anti-adrenergic action. This confirms the recent findings of Carmeliet (1985) and of Kato *et al.*, (1986) for guinea-pig and rabbit ventricle.

In guinea-pig atrial muscle, in contrast, a significant class III effect was observed only for D-sotalol and only at the highest concentration studied (50 μM). Non-significant trends towards a prolongation of action potential duration were seen for DL-sotalol, and it is not possible from the current data to compare accurately the potencies of D- and DL-sotalol on this tissue. There can be no doubt, however, that both compounds exhibit considerably greater potency on guinea-pig ventricular fibres than on atrial fibres. Similar differences (for DL-sotalol) were noted in early studies (Singh & Vaughan Williams, 1970; Strauss *et al.*, 1970), and more recently, Kato *et al.*, (1986), found significant class III effects for D- and L-sotalol at concentrations of 10 μM and above on canine ventricular muscle but only at 100 μM on rabbit atrium. The present study confirms this difference in tissue sensitivity within a single species.

Plasma concentrations of DL-sotalol in patients on long-term oral therapy with this agent are usually less than 10 μM and certainly below 20 μM (Elonen *et al.*, 1979; Neuvonen *et al.*, 1981). Levels up to approximately 40 μM have been found in patients immediately following acute intravenous injection of DL-sotalol (Nademanee *et al.*, 1985) but it is unlikely that the concentrations would remain so high for long (Campbell *et al.*, 1985). Indeed, severe toxicity has been described at blood levels of 25 μM and 53 μM following deliberate overdosage (Elonen *et al.*, 1979). It would thus seem unlikely that potentially antiarrhythmic effects seen only at 50 μM or above would be of any clinical relevance, a point not specifically addressed by other workers.

Effects on human atrial cells

DL-Sotalol has been shown to be beneficial in the treatment of atrial tachyarrhythmias in man at concentrations below 10 μM (Campbell *et al.*, 1985) and to prolong human atrial repolarization in similar concentrations (measured as monophasic action potential duration; Echt *et al.*, 1982; Hayward & Taggart, 1986). These facts strongly suggest the possibility that human atrial cells may be more sensitive than those of rabbits or guinea-pigs to the class III actions of solatol. This has been confirmed by the present study. Increases of 8.7% and 10% in APD_{90} were seen with DL-sotalol 10 μM and D-sotalol 10 μM, respectively. These are consistent with increases in atrial monophasic action potential duration of 16% seen by Echt *et al.* (1982) and 6–8% found by Hayward & Taggart (1986) following acute administration of DL-sotalol intravenously. Blood levels were presented only for the first of these studies where peak plasma sotalol levels were approximately 5–9 μM. Acute therapy with other β-adrenoceptor blocking agents does not prolong atrial action potential duration (Echt *et al.*, 1982).

Thus DL-sotalol and D-sotalol have a significant class III effect on human atrium at clinically relevant concentrations. It is reasonable to assume that this action contributes to the proven efficacy of sotalol in atrial tachyarrhythmias (Campbell *et al.*, 1985). Speculation as to the ionic current mechanisms for the differential sensitivity to sotalol of human atrial cells compared to guinea-pig and rabbit atria is beyond the scope of the present study.

Effects on guinea-pig sinus node cells

Both DL- and D-sotalol produced dose-dependent, reversible increases in sinus node cycle length. In both cases this effect was almost entirely attributable to prolongation of repolarization although DL-sotalol

did significantly reduce the slope of phase 4 depolarization as well. Kato *et al.* (1986) have recently reported very similar findings (apart from a lack of any effect on phase 4) for rabbit sinoatrial node cells. The data from these two studies contrast with the earlier observations of Strauss *et al.* (1970) in which no significant depression of rabbit sinus rate was found at concentrations of sotalol less than 100 μM. These workers did not record intracellular potentials from sinus node cells and no definite explanation for the differences can be given.

The effects we have observed on sinus node potentials are consistent with the ability of D- and L-sotalol to block the repolarizing potassium current (i_K) shown for rabbit Purkinje fibres by Carmeliet (1985). It seems likely that a similar outward potassium current (also called i_K) is largely responsible for repolarization in sinus node fibres (Noble & Noble, 1984) and it is reasonable to speculate that the mechanism for the drug effects are the same on both tissues.

Whatever the cellular mechanism, it is of considerable clinical relevance to know that D-sotalol has comparable effects to DL-sotalol on sinus cycle length *in vitro*. This explains the reduction in heart rate noted in a preliminary clinical report on the use of this agent (Rowland *et al.*, 1985). Sinus node depression can be a clinical problem with DL-sotalol (Campbell *et al.*, 1985) and it will be of interest to see whether the D-isomer, which shares the effects of DL-sotalol on repolarization but does not share the anti-adrenergic effects, will give rise to less symptomatic sinus node depression in large-scale clinical use.

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