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Differing electrophysiological effects of class IA, IB and IC antiarrhythmic drugs on guinea-pig sinoatrial node

Terence Campbell

School of Physiology & Pharmacology, University of New South Wales, Kensington 2033, Sydney, Australia

1 Standard microelectrode techniques were used to study the effects of class IA (quinidine, disopyramide, procainamide), IB (lignocaine, mexiletine, tocainide) and IC (flecainide, encainide, lorcainide) antiarrhythmic drugs on action potentials in spontaneously beating sino-atrial node cells from guinea-pigs.

2 The IA drugs all produced significant slowing of spontaneous rate in therapeutic concentrations. The IB agents did so only in concentrations well above therapeutic levels and the IC drugs were of intermediate potency.

3 All nine drugs markedly slowed the repolarization rate and this was the major mechanism of sinus slowing for the IA and IC compounds. The IB drugs shared this effect but prolongation of phase 4 by reduction of the slope of diastolic depolarization was also a prominent feature of their action.

Introduction

Drugs that act primarily by depressing the fast inward sodium current of the cardiac action potential, 'Class I' agents, comprise the largest and most disparate group of antiarrhythmic compounds (Vaughan Williams, 1980). They are commonly subclassified into group IA agents as quinidine, disopyramide and procainamide and group IB, including lignocaine, tocainide and mexiletine (Singh & Hauswirth, 1974). More recently a third group, IC, of compounds such as flecainide, encainide and lorcainide has been proposed (Harrison *et al.*, 1981). There is good evidence for this subgrouping based both on differences in clinical electrophysiological properties and on differences in their kinetics of interaction with the fast sodium channel *in vitro* (Harrison *et al.*, 1981; Vaughan Williams, 1984).

Effects on resting heart rate are not a prominent side effect of class I agents but most of them have the capacity to produce significant sinus node depression in some patients, particularly those with pre-existent sinus node dysfunction (see Discussion). This effect is very unlikely to be due solely to depression of the fast sodium current (I_{Na}), since this is largely inactivated in specialized sino-atrial cells (Brown, 1982). Tetrodotoxin (which selectively blocks I_{Na}) does have some depressant effect on the sinus node, (Yamagishi & Sano, 1966), and a small contribution to the effects of class I drugs from depression of I_{Na} cannot be ruled out.

The aim of the present study then, was to investigate the mechanisms by which class I antiarrhythmic drugs depress the automaticity of the sino-atrial node of the guinea-pig, with a particular view to elucidating any differences in this regard between the three subgroups.

Methods

Guinea-pigs of either sex weighing 500–800 g were killed by cervical dislocation and their hearts quickly removed. The right atrium was isolated and a portion of the posterior wall dissected out and pinned to the base of a bath (volume 0.5 ml). The borders of this segment 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°C ± 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. Preparations were allowed to equilibrate for 1 to 3 h before taking recordings and, unless otherwise stated, were allowed to beat spontaneously throughout the experiment. Action potentials were recorded from the endocardial surface by conventional glass microelectrodes filled with 3M KCl (impedance 15–40 megaohm) and coupled to a high input impedance d.c. amplifier

(Neurolog NL102G). During the equilibration period, the area of the sinoatrial node (SAN) was located by exploring with the microelectrode in the area adjacent to the crista terminalis and the superior vena cava (Grant & Strauss, 1982). Sinoatrial cells were defined as those with maximum diastolic potential less than −70 mV and with marked spontaneous diastolic (phase 4) depolarization followed by a smooth transition into a relatively slow upstroke (phase 0) with a maximum rate of depolarization below $10\,V\cdot s^{-1}$ (Brown, 1982; Grant & Strauss, 1982). Experiments were started only after stable impalement of such a cell had been maintained for at least 15 min. Except where otherwise stated, each experiment was performed during continuous impalement of a single SAN cell. Action potentials were analysed before exposure to drug (control), during exposure and after returning to superfusion with control solution. On the basis of the time taken to achieve maximum effect and maximum recovery from drugs, exposure times were 20 min for lignocaine, tocainide and mexiletine and 30 min for the other 6 drugs. Wash-off times for these two groups were 30 min and 60 min respectively.

Analysis of recordings

The action potential was monitored continuously on a storage oscilloscope. Analysis of selected 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. On command, a machine code programme acquires 1000, 10-bit samples of the SAN action potential at a rate of 1KHz, and saves them in memory. A BASIC programme initiates the machine language programme, waits for data acquisition and then takes the raw amplitude samples from memory for subsequent analysis during which the following parameters are 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 of phase 4, cycle length, the slope of phase 4 depolarization and the maximum slopes of phase 0 depolarization and of repolarization (Figure 1).

Drugs were kindly supplied by the following companies: Astra Pharmaceuticals (lignocaine, tocainide), Boehringer Ingelheim (mexiletine), Roussel (disopyramide), Riker Laboratories (flecainide), Bristol Myers Company (encainide) and Janssen Pharmaceuticals (lorcainide).

Data are expressed as mean ± standard deviation and significance of differences between means was assessed by Student's paired *t* test.

Results

Effects on spontaneous cycle length

In this series of experiments, which was performed without continuous intracellular recording, a range of concentrations was used to document prolongation of spontaneous cycle length by each drug (Table 1). As can be seen, all of the drugs produced significant dose-dependent increases in cycle length which reversed at least partially within 30–60 min of wash-off.

The IA compounds appeared most potent in this regard. All three of them significantly prolonged cycle length at levels within the therapeutic range and quinidine and disopyramide did so even in sub-therapeutic concentrations. None of the IB drugs prolonged cycle length by more than 5% in therapeutic doses (and this was statistically significant only for tocainide). The IC agents showed intermediate effects with flecainide and encainide producing significant prolongation (29% and 15% respectively) in the high therapeutic range and lorcainide only above this range.

Action potential effects: amplitude and rate of depolarization (phase 0)

The control values for the 68 sino-atrial node cells from which intracellular recordings in the presence of drugs were taken, are given in Table 2.

No drug significantly altered take-off potential. The class IB agents had no effects on action potential amplitude. All the IA and IC drugs produced small

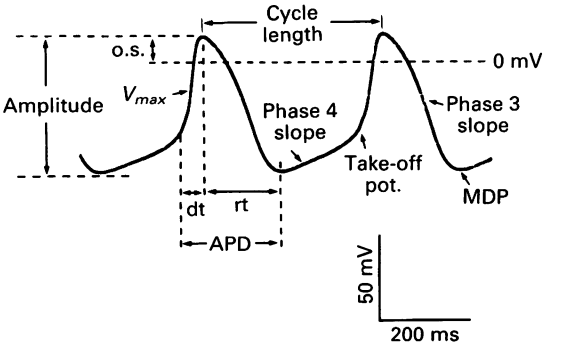

Figure 1 Diagram of consecutive sinus code cell action potentials illustrating the measurements made by the computer programme. Abbreviations: APD – action potential duration; dt – depolarization time; MDP – maximum diastolic potential; o.s. – overshoot (or peak potential); rt – repolarization time; V_{max} – maximum rate of depolarization. The phase 4 time (not illustrated) is measured from the maximum diastolic potential to the following take-off point.

Table 1 Effects of drugs on spontaneous cycle length in guinea-pig sinoatrial node

Drug	*Concentration* (μM) *and cycle length* (ms)					*Therapeutic concentration* (μM
Quinidine	0	1	5	10	Wash 60 min	5–15
($n = 6$)	316 ± 23	343 ± 39*	368 ± 56*	387 ± 77*	355 ± 32*	
Disopyramide	0	5	10	20	Wash 60 min	8–22
($n = 7$)	339 ± 48	360 ± 47*	392 ± 56**	408 ± 58**	333 ± 50	
Procainamide	0	25	50	100	Wash 60 min	14–40
($n = 9$)	339 ± 36	370 ± 46*	387 ± 47†	416 ± 52+	341 ± 31	
Lignocaine	0	25	50	100	Wash 30 min	9–26
($n = 7$)	324 ± 39	320 ± 38	335 ± 36	368 ± 36*	319 ± 44	
Mexiletine	0	10	20	50	Wash 30 min	3.5–9.3
($n = 7$)	317 ± 34	331 ± 40	343 ± 41*	373 ± 49**	317 ± 32	
Tocainide	0	50	200	400	Wash 30 min	22–80
($n = 7$)	319 ± 31	335 ± 36†	377 ± 52†	441 ± 68†	326 ± 27	
Flecainide	0	0.5	2	5	Wash 30 min	0.5–2.0
($n = 15$)	323 ± 17	344 ± 15	391 ± 15†	424 ± 15†	389 ± 16†	
Encainide	0	1	2	10	Wash 30 min	0.2–2.0
($n = 9$)	311 ± 41	332 ± 40*	359 ± 38**	385 ± 41†	316 ± 43	
Lorcainide	0	1	2	5	Wash 30 min	0.3–1
($n = 7$)	319 ± 35	324 ± 33	345 ± 36**	370 ± 40**	343 ± 41**	

Exposure times at each concentration = 20 min.
*$P < 0.05$;**$P < 0.01$; †$P < 0.001$; significance of difference from control.

falls in amplitude ranging from 2.1 mV to 9.3 mV. These were significant only for disopyramide (79.4 ± 8 mV to 70.1 ± 9 mV; $P < 0.05$), encainide (76.4 ± 8 to 68.9 ± 8 mV; $P < 0.05$) and lorcainide (71 ± 9 to 66 ± 8 mV; $P < 0.01$). In each case the reduction was due to a combination of falls in overshoot voltage and maximum diastolic potential.

All nine drugs showed a trend to reduce the maximum rate of depolarization in phase 0 (V_{max}) but this reached statistical significance only for encainide (3.0 ± 1.2 to 2.0 ± 0.5 Vs^{-1} $P < 0.05$) and disopyramide (7.7 ± 2.1 to 4.9 ± 1.5 Vs^{-1}; $P < 0.05$).

Action potential effects: repolarization and phase 4

The increases in cycle length were in all cases produced by a combination of prolongation of action potential duration (largely due to slowing of the rate of repolarization) and a depression of the rate of spontaneous phase 4 depolarization (Table 3). The slowing of repolarization (phase 3) was less marked for the IB drugs than for IA and IC though still statistically significant (Figure 2). This is despite the fact that the IB drugs were studied at concentrations ranging from 5.7 to 7.8 × mid-therapeutic concentrations (compared to 1.0 to 3.7 × mid-therapeutic concentration for the IA drugs and 4.0 to 10.0 for IC). In two preliminary experiments with lower concentrations of mexiletine (10 and 20 μM) and tocainide (100 and 200 μM), marked flattening of the phase 4 slope was observed with only small increases (mexiletine) or no change (tocainide) in repolarization time.

Reduction of spontaneous phase 4 depolarization was observed with all 9 drugs (Table 3). However, this effect did not achieve statistical significance for the IA compounds which were (as noted above) studied at

Table 2 Control values for 68 sinus node cells

Cycle length (ms)	321 ± 33	Action potential duration (ms)	190 ± 15
Overshoot (mV)	12.9 ± 5.4	Depolarization time (ms)	38 ± 6
Maximum diastolic potential (mV)	−62.5 ± 5.1	Repolarization time (ms)	153 ± 14
Amplitude (mV)	75.3 ± 7.4	Phase 3 slope (Vs^{-1})	−0.97 ± 0.15
Take-off potential (mV)	−40.9 ± 6.4	Phase 4 duration (ms)	131 ± 27
$\dot{V}_{max}$ (Vs^{-1})	3.8 ± 3.7	Phase 4 slope (mVs^{-1})	134 ± 51

Values are means s.d.; $\dot{V}_{max}$ = maximum rate for depolarization.
Refer to Figure 1 for definition of other parameters.

Table 3 Effects of drugs on cycle length, rate of repolarization (phase 3 slope) and rate of diastolic depolarization (phase 4 slope)

	Cycle length (ms)			*Phase 3 slope* (Vs^{-1})			*Phase 4 slope* (mVs^{-1})		
	Control	*Drug*	*Wash*	*Control*	*Drug*	*Wash*	*Control*	*Drug*	*Wash*
Quinidine 10 μM ($n = 5$)	296 ± 14	358 ± 23**	310 ± 14	−0.94 ± 0.17	0.63 ± 0.06**	0.95 ± 0.09	160 ± 43	125 ± 32	156 ± 43
Disopyramide 20 μM ($n = 5$)	309 ± 27	377 ± 62*	315 ± 42	−1.0 ± 0.23	−0.68 ± 0.16**	0.89 ± 0.24	129 ± 48	109 ± 62	141 ± 67
Procainamide 100 μM ($n = 6$)	327 ± 16	370 ± 13	316 ± 13†	−0.91 ± 0.13	−0.65 ± 0.06	0.91 ± 0.14†	120 ± 25	107 ± 35	132 ± 55
Lignocaine 100 μM ($n = 7$)	310 ± 51	356 ± 68*	316 ± 50	−1.04 ± 0.15	−0.85 ± 0.20**	−1.10 ± 21	141 ± 69	111 ± 60*	172 ± 73
Mexiletine 50 μM ($n = 6$)	297 ± 18	350 ± 29†	310 ± 24	−0.99 ± 0.13	−0.84 ± 0.11**	−0.98 ± 0.14	167 ± 97	120 ± 38*	151 ± 54
Tocainide 400 μM ($n = 8$)	316 ± 32	374 ± 42†	312 ± 33	−0.94 ± 0.14	−0.77 ± 0.16**	−0.98 ± 0.14	135 ± 53	85 ± 26**	142 ± 59
Flecainide 5 μM ($n = 7$)	325 ± 31	371 ± 38*	332 ± 21	−0.99 ± 0.18	−0.71 ± 0.10**	−0.91 ± 0.06	131 ± 40	108 ± 50*	130 ± 36
Encainide 10 μM ($n = 6$)	338 ± 31	421 ± 66**	345 ± 36	−1.07 ± 0.08	−0.66 ± 0.12**	−1.04 ± 0.07	125 ± 34	98 ± 41**	123 ± 30
Lorcainide 5 μM ($n = 7$)	341 ± 34	419 ± 57**	351 ± 33	−0.94 ± 0.15	−0.69 ± 0.14**	−0.92 ± 0.15	101 ± 20	72 ± 27*	106 ± 21

Means ± s.d. in control and after 20–30 min drug exposure and 30–60 min wash-off. Significance symbols as for Table 1.

relatively lower concentrations than the other agents.

These differences are further illustrated by Table 4 in which are shown the relative contributions to the overall increase in cycle length produced by effects on phase 0 (depolarization), phase 3 (repolarization) and phase 4 (diastole). The IA drugs increased cycle length largely by prolonging repolarization. Effects on repolarization and diastolic depolarization were both prominent with IB compounds. The IC agents (with the possible exception of lorcainide) most closely resemble the IA action.

Discussion

The distinction between IA, IB and IC drugs is well known to clinical cardiologists. The major electrophysiological differences between the subgroups are that IA drugs in therapeutic concentration tend to depress $\dot{V}_{max}$ and hence conduction of all action potentials and to prolong their duration, IB drugs selectively depress action potentials from partly depolarized cells and premature action potentials and tend to decrease the duration of these potentials and IC drugs markedly depress $\dot{V}_{max}$ but produce only minor increases in action potential duration (Harrison *et al.*, 1981; Harrison, 1985). As has been noted, much of this depends on differences in the way the drugs interact with the fast sodium channels (Campbell, 1983; Vaughan Williams, 1984), which are unlikely to be of relevance in a study of sinus node cells. The IB drugs studied do not normally produce slowing of sinus node automaticity, but there have been several reports of significant sinoarterial depression produced by therapeutic concentrations of lignocaine and mexiletine (usually in patients with sick sinus syndrome) (Lippestad & Forfang, 1971; Roos *et al.*, 1976). Such depression is seen somewhat more often with IA drugs (Birkhead & Vaughan Williams, 1977; Dhingra & Rosen, 1979). Furthermore the anticholinergic properties of quinidine and disopyramide (Mirro *et al.*, 1981) undoubtedly contribute to the low incidence of clinical sinus node dysfunction seen with these drugs. This has been confirmed by recent studies on cardiac transplant patients, whose denervated hearts routinely respond to these drugs with significant increases in spontaneous cycle length (Mason *et al.*, 1977; Bexton *et al.*, 1984). Procainamide (which has virtually no anticholinergic activity) appears to be less liable to depress the sinus node than the other IA compounds studied, although isolated reports exist of such effects (Kim & Friedman, 1979). Effects on resting heart rate have not been a prominent feature of the IC agents in clinical use although all three drugs studied have been reported to reduce it significantly in some studies, especially in patients with pre-existing sino-atrial node disease (Dibianco *et al.*, 1982; Singh *et al.*, 1984; Hellestrand *et al.*, 1984).

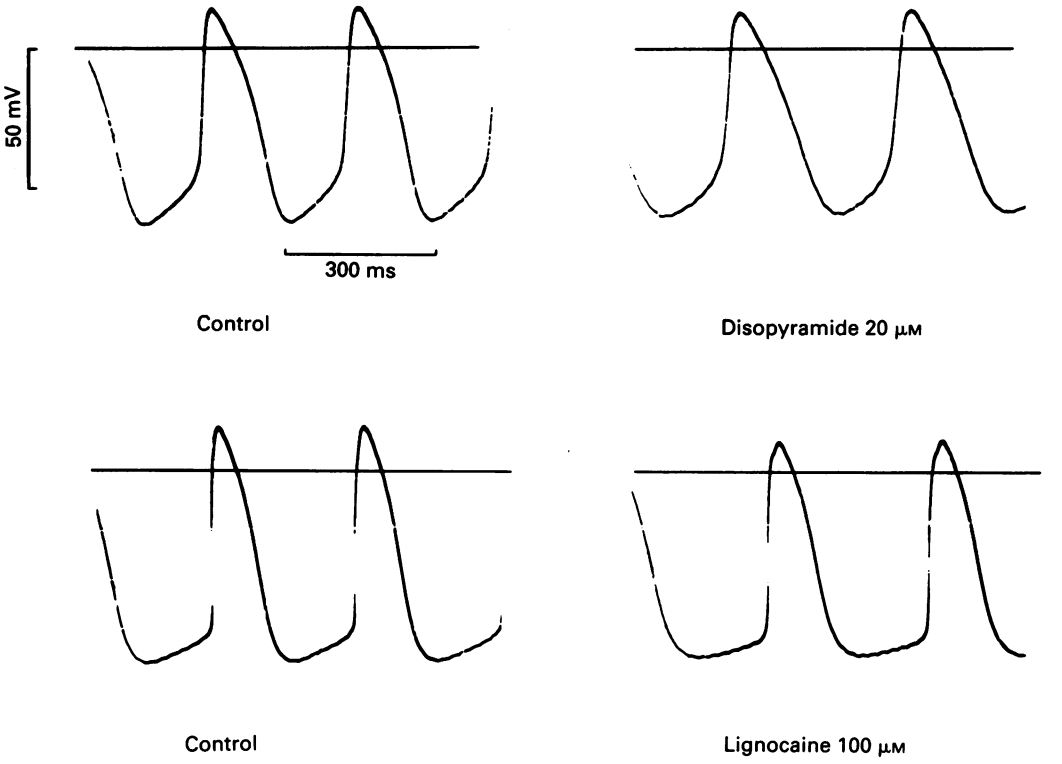

Figure 2 Contrasting effects on sinus node action potentials of disopyramide (IA drug; 20 μM) and lignocaine (IB drug; 100 μM). Disopyramide increases cycle length predominantly by prolonging repolarization time. Lignocaine does this also to a small extent but also flattens the slope of phase 4 depolarization.

This difference between the subgroups was evident in the present study, (Table 1). All the IA drugs produced significant prolongation of cycle length in therapeutic (and even sub-therapeutic) concentrations, whereas the IB drugs required concentrations well above their therapeutic ranges to produce comparable effects (tocainide prolonged cycle length 5% at 50 μM).

The IC agents were of intermediate potency with flecainide and encainide producing significant prolongation in the high therapeutic range and lorcainide only at toxic levels.

When these differences between subgroups are analysed in terms of actions of intracellular sinus node potentials, it seems possible that they may be more than simply quantitative. IA drugs produce almost all their effect by slowing repolarization (phase 3) and hence increasing action potential duration. The IB drugs on the other hand produce a large proportion of their cardiac slowing by flattening the slope of spontaneous diastolic depolarization (phase 4) and hence prolonging diastole. Furthermore, in two preliminary experiments with lower concentrations of mexiletine and tocainide, marked flattening of the phase 4 slope was observed with only minor changes in repolarization time. In other words, this action on phase 4 may be the major effect of IB drugs in clinically relevant concentrations, with marked slowing of repolarization appearing only at toxic levels. The IC agents once again occupy an intermediate position with significant effects (in clinically relevant concentrations) both on repolarization and, especially for lorcainide, on phase 4.

In the absence of voltage-clamp studies, any discussion of the ionic current mechanisms is purely speculative. Repolarization in sinus node cells is produced largely by outward potassium currents (Brown, 1982) and it seems reasonable to suggest that the drugs studied may be depressing this process.

The idea that some class I antiarrhythmic drugs might block K^+ channels as well as Na^+ channels is not new. There is good evidence for such an effect for quinidine in frog atrial muscle (Ducouret, 1976), and cat and human ventricular muscle (Nawrath, 1981;

Table 4 Effects of drugs on components of sinus node potentials

	Quinidine	*Disopyramide*	*Procainamide*	*Lignocaine*	*Mexiletine*	*Tocainide*	*Flecainide*	*Encainide*	*Lorcainide*
Δ Cycle length (ms)	62	68	43	46	53	58	46	83	76
Δ Depolarization Time (ms)	7	13	1	1	3	4	6	11	10
Δ Repolarization time (ms)	46	53	41	24	32	30	37	60	46
Δ Phase 4 duration (ms)	4	2	1	21	18	24	6	11	20

Δ = increase in the value of.

Nawrath & Eckel, 1979), and for disopyramide in rabbit atrioventricular node cells (Nishimura *et al.*, 1982) The latter two drugs exert their effects on K^+ currents at concentrations in or near the therapeutic range, whereas flecainide, encainide and lorcainide appear to have significant actions on repolarization currents only in concentrations above their accepted therapeutic ranges. This is consistent with the more marked effects of quinidine and disopyramide on action potential duration, on QT interval (determined from the surface electrcardiogram) and on refractory periods in therapeutic concentrations (Campbell, 1983). Finally, Satoh & Hashimoto (1984) have very recently published direct voltage-clamp evidence for depression of i_K in rabbit sinus node cells by very high concentrations of lignocaine (approximately 200–400 μM).

It is even more difficult to propose a mechanism for the depression of phase 4 spontaneous depolarization seen in the present experiments. This is because of the complex and still controversial nature of currents underlying this 'pacemaker' activity (Brown, 1982; Noble & Noble, 1984). Apart from deactivation of outward K^+ current, activation of the slow inward (calcium) current (largely responsible for phase 0 depolarization) and possibly a newly-described inward current (i_f or i_h) activated on hyperpolarization and carried largely by sodium are thought to be involved. Marked depression of the calcium current might be expected to produce greater reduction in phase 0 $\dot{V}_{max}$ than was seen in the present study, though some contribution from such an effect is possible. There is direct evidence for depression of i_f by high concentrations of lidocaine (Satoh & Hashimoto, 1984) but not enough is yet known about this current to be sure of the relevance of that observation.

Whatever the ultimate ionic mechanisms, it is apparent that although all nine drugs suppressed sinus node activity, there were differences between the subgroups IA, B, C, both in terms of the concentration ranges in which these effects were seen and in the changes induced in sinus node action potentials. These data, therefore, provide further justification, in terms of cellular electrophysiological effects, for the subdivision of class I antiarrhythmic drugs into three groups.

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