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Effects on rabbit cardiac potentials of aprindine and indecainide, a new antiarrhythmic agent, in normoxia and hypoxia

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1 Intracellular potentials were recorded from rabbit atria, cardiac Purkinje cells and papillary muscles before and after exposure to various concentrations of indecainide. The effects of aprindine also were studied in the atrial preparations.

2 Both drugs depressed the maximum rate of depolarization (MRD) in a dose-related manner, indecainide being approximately ten times more potent than aprindine.

3 Aprindine caused a dose-related bradycardia, but indecainide had no significant effect on sinus node frequency.

4 Indecainide had a dose-related negatively inotropic effect in normal, half-normal and twice-normal extracellular calcium concentrations.

5 Indecainide shortened action potential duration (APD) in atrium and Purkinje cells but prolonged APD to 50% repolarization in ventricular muscle.

6 The actions of indecainide were extremely persistent. No significant recovery of MRD was observed after pauses in stimulation of up to 16 s.

7 Indecainide had no effect on effective refractory period (ERP) measured by interpolated premature stimuli.

8 Indecainide is therefore categorized as a Class 1c antiarrhythmic agent.

9 The effects of both aprindine and indecainide on MRD were increased in hypoxic atria. Conduction velocity in hypoxic atria exposed to indecainide was greater than in controls, however, suggesting the possibility of improved cell-to-cell coupling.

Introduction

Aprindine was introduced a decade ago as a very potent class 1 antiarrhythmic agent, reported to be superior to procainamide and quinidine in cross-over studies of patients with stable ventricular arrhythmias (Van Durme *et al.*, 1974): it has since proved useful also in the treatment of supraventricular arrhythmias (Singh, 1981). It widened QRS and prolonged His-ventricular (H–V) conduction time in man (Kesteloot *et al.*, 1973; Singh, 1981); *in vitro* it shortened the action potential duration (APD) in Purkinje fibres but caused no corresponding shortening of the effective refractory period (Verdonck *et al.*, 1974; Carmeliet & Verdonck, 1974; Steinberg & Greenspan, 1976). The action of aprindine was persistent, recovery in drug-free solution being very slow. It also had a long elimination half-life *in vivo* (about 27 h; Fasola & Carmichael, 1974).

Indecainide is a new compound, the structure of which is illustrated in Figure 1. It has been developed as a possible replacement for aprindine, serious toxic effects of which have been reported (Van Leeuwen & Meyboom, 1976). In order to characterize indecainide, we have studied its electrophysiological and other effects in various tissues of the rabbit heart and have in some cases made direct comparisons with aprindine.

Methods

Intracellular potentials

Rabbits of either sex, weighing 700–1200 g, were injected with 200 units sodium or lithium heparin solution, stunned and their hearts rapidly removed.

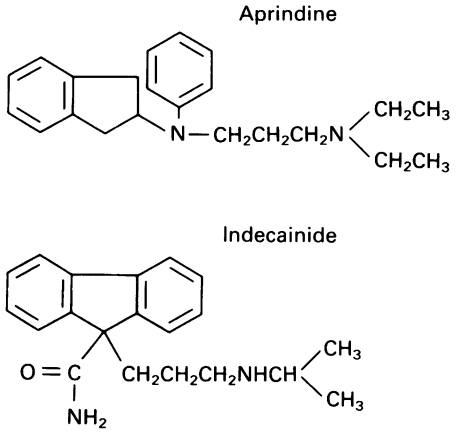

Figure 1 Structures of aprindine and indecainide.

Atrial preparations The atria were suspended horizontally in an organ bath. Intracellular potentials were recorded from the crista terminalis of the right atrium: contractions were measured with a strain gauge.

Ventricular preparations After removal of the heart, the free walls of the atria and left ventricle were excised, the interatrial septum and atrioventricular (A–V) node being left intact. The right ventricular free wall was peeled back from its posterior border, exposing the right endocardial surface of the interventricular septum and the endocardial surface of the right ventricular free wall. The preparation was supported on wire mesh about 2 mm above the base of the organ bath, to permit free circulation of solution above and below the tissue. The preparations were stimulated by an electrode on the atrial remnant, or on the bundle of His if conduction through the A–V node was blocked, as occurred occasionally. Each preparation was exposed to only two of the three concentrations of indecainide: in the Tables of results, therefore, separate control values have been presented appropriate for the drug concentrations employed.

All preparations were kept in an externally oxygenated organ bath (Szekeres & Vaughan Williams, 1962) at 32°C, and paced at a frequency about 10% higher than the spontaneous frequency (in practice, atrial preparations were invariably stimulated at 2.6 Hz; the range for the ventricular preparations was 2.6–3.0 Hz). The bathing solution contained (mmol l^{-1}): NaCl 125, KCl 5.6, $NaHCO_3$ 25, $NaHPO_4$ 0.4, $MgCl_2$ 1.0, $CaCl_2$ 2.16 and glucose 11. Intracellular potentials, measured with 3 M-KCl-filled glass electrodes, and contractions, when measured, were recorded on magnetic tape for subsequent analysis by computer (Vaughan Williams, 1977). Tissues were exposed to each drug concentration for 40 min before records were taken; higher concentrations were then admitted to the bath without intermediate washing; after exposure to the highest concentrations, 'recovery' measurements were made after washing for 60 and 90 min in drug-free solution.

In some experiments, atrial preparations were exposed to hypoxia for 15 min periods by equilibrating the bathing fluid with 20% O_2, 75% N_2 and 5% CO_2, each period being followed by 25 min perfusion with the control solution equilibrated with 95% O_2 and 5% CO_2. Successive exposures to hypoxia had cumulative effects (Millar & Vaughan Williams, 1982) and so different preparations were used for control and drug experiments.

Isolated atria: effects of isoprenaline and changes in extracellular calcium concentration

Isolated atria, prepared as above, were suspended vertically in directly oxygenated physiological saline at 32°C. Solutions containing various concentrations of calcium were run into the bath from the bottom, and excess fluid was removed from the top by suction, to avoid disturbance of the tissue by exposure to air. Spontaneous contractions were displayed on a Devices 2-channel paper recorder. For measurement of changes in developed tension the atria were paced at constant frequency (2.6 Hz).

Local anaesthesia

Sciatic nerves were removed from pithed frogs, and the perineural sheaths stripped from the central portions. The nerve was enclosed in a three-compartment chamber: supramaximal stimuli were applied at the proximal end, and action potentials recorded from the distal end, the nerve being supported on platinum wires in moist air. Various concentrations of procaine or indecainide were applied to the stripped portion of the nerve, immersed in physiological saline in the central chamber, as previously described (Dohadwalla *et al.*, 1969).

Statistical treatment

Results have been expressed as means ± standard error of the mean (s.e.mean) and the significance of differences has been calculated by Student's *t* test, the pooled results of all experiments being treated as a single population.

The control values of some parameters, in particular action potential duration (APD) and maximum rate of depolarization (MRD), varied considerably in different animals, so that the significance of drug effects

was less apparent when the results were pooled. As an additional procedure, therefore, values of MRD and APD in each set of control and treated results were expressed as a percentage of the control mean in each individual experiment. Variance was then calculated in the usual way from these percentages, and the significance of differences estimated in relation to the control mean from all experiments, thus eliminating the variation between animals.

All atrial and most ventricular preparations were stimulated at 2.6 Hz: preparations with higher spontaneous frequencies were not included in the calculation of mean values of action potential duration.

Drugs used

Aprindine and indecainide (LY135837) were gifts, which are gratefully acknowledged, from Lilly Research. Other drugs were obtained commercially.

Results

1. Experiments related to restriction of sodium current (Class 1 action)

(a) Depolarization of frog nerve Indecainide had approximately the same local anaesthetic potency as procaine. The mean concentrations (± s.e.mean) required to reduce the amplitude of the compound action potential to 50% of its control value were 0.62 ± 0.04 and 0.79 ± 0.04 mmol l^{-1} ($n = 5$) of indecainide and procaine respectively, the dose-response curves being parallel. Both drugs exerted their maximum effect within 10–15 min. On being washed with drug-free solution, the nerves recovered fully from procaine within 15 min, but recovery from indecainide was not complete after 90 min.

(b) Depolarization of cardiac muscle

Atria Both indecainide and aprindine (at concentrations including the range observed in the plasma of treated patients (Van Durme *et al.*, 1974)) depressed action potential amplitude (APA), MRD and conduction velocity in a dose-related manner (Table 1). There was no significant effect on resting potential. The significant changes have been indicated as percentages, for ease of comparison, and it is apparent that indecainide is approximately ten to twenty times more potent than aprindine as a class 1 drug on a molar basis.

The effects of aprindine were partially reversed after washing the tissues for 90 min in drug-free solution, but there was no statistically significant recovery from the effects of indecainide after the same period.

Table 1 Effects of aprindine and indecainide on atrial action potential amplitude (APA), maximum rate of depolarization (MRD) and conduction velocity

Aprindine								
Concentration (mol l^{-1})		0	1.6×10^{-6}	Δ %	3.2×10^{-6}	Δ %	6.4×10^{-6}	Δ %
	n	51	36		39		27	
APA (mV)		94.7 (0.8)	93.6 (1.0)		92.2* (1.0)	− 2.5	83.7** (1.5)	− 11.5
MRD ($V s^{-1}$)		172.5 (6.4)	143.6* (10.5)	− 16.8	126.4*** (10.8)	− 26.7	92.6*** (7.7)	− 46.3
Conduction velocity ($m s^{-1}$)		0.25 (0.01)	0.21 (0.01)		0.21* (0.01)	− 16.0	0.18*** (0.01)	− 28.0
Indecainide								
Concentration (mol l^{-1})		0	8.7×10^{-8}		2.9×10^{-7}		8.7×10^{-7}	
	n	24	24		27		22	
APA (mV)		95.3 (1.4)	89.4* (1.5)	− 6.3	86.1*** (1.2)	− 9.7	87.7** (1.5)	− 8.1
MRD ($V s^{-1}$)		205.3 (10.1)	167.0* (8.5)	− 18.7	121.1*** (6.8)	− 41.0	117.0*** (6.1)	− 43.0
Conduction velocity (ms^{-1})		0.43 (0.02)	0.38 (0.02)		0.34* (0.01)	− 20.9	0.28*** (0.01)	− 34.9

Values are means ± (s.e.mean).
n = number of fibres from 5 experiments.
Statistical significance of differences: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$

Electrical threshold: The threshold voltage at which atria would follow a pacing stimulus applied at 2.6 Hz was not significantly changed by either drug.

Ventricle Results illustrating the effects of indecainide on ventricular myocardium and Purkinje cells are presented in Table 2: they are similar to those obtained from atrial myocardium, though the effects at each concentration are proportionately less in ventricular tissues. The effects of aprindine on Purkinje cells and ventricular muscle were extensively investigated by Verdonck *et al.* (1974), and have not been studied here.

There was considerable variation between animals in MRD, so that although there is a clear dose-related depressant trend apparent in Table 2 (− 9.9, − 28.4 and − 41.3% in papillary muscle, and − 14.6 and − 26.5% in Purkinje cells), only at the higher concentrations were the figures statistically significant (plus signs in Table 2). If, however, the between-animal variation was eliminated the levels of significance were often higher (asterisks in Table 2).

Conduction velocity in the ventricular pathway between the His bundle and the papillary muscle was reduced by indecainide: concentrations of 2.9×10^{-7} and 8.7×10^{-7} mol l^{-1} reduced the conduction velocity in four preparations stimulated at the Bundle of His from a control value of 0.363 ± 0.011 ms^{-1} to 0.340 ± 0.005 ($P < 0.05$) and 0.307 ± 0.006 ms^{-1} ($P < 0.001$) respectively (mean of 30 fibres). Depression of H–V conduction in man is characteristic of group 1c compounds.

Recovery from the effects of the drug was very slow: after 90 min washing in drug-free solution following exposure to the highest dose of indecainide, MRD had recovered to only 79% of its control value in Purkinje cells and 63% in papillary muscle.

Effects of trains of stimuli at 2Hz Previous studies indicated that class 1 drugs could be subdivided into groups (b), (a) and (c) on the basis of fast, medium and slow onset/offset kinetics of frequency-dependent block of fast inward current (as discussed in detail later). It has already been shown that during pacing at constant frequency concentrations of indecainide of 2.9×10^{-7} and 8.7×10^{-7} mol l^{-1} caused steady-state reductions of MRD in papillary muscles of 12.8 and 25.3%, respectively. In similar experiments, after steady-state block at these concentrations had been established, the muscles were left quiescent for 5 min, and were then stimulated at 2.0 Hz in trains of 16 stimuli. It was found that during each train no further significant depression of MRD occurred. At the end of each train, stimulation was interrupted for increasing periods. It was found that pauses of stimulation of up to 16 s revealed no recovery of MRD. It was concluded that the onset/offset kinetics of indecainide were so slow that a more extended study of its

Table 2 The effects of indecainide on intracellular action potentials in Purkinje cells and ventricular myocardium

Concentration (mol l^{-1})	*n*	*Resting potential* (mV)	*Action potential amplitude* (mV)	*MRD* (Vs^{-1})
(A) *Papillary muscle*				
Control	52	− 78.1 (0.5)	99.3 (0.6)	163.9 (5.6)
2.9×10^{-7}	46	− 77.4 (0.6)	99.2 (0.7)	147.6 (6.1)***
Control	44	− 77.9 (0.5)	99.4 (0.7)	166.0 (6.1)
8.7×10^{-7}	30	− 77.3 (0.7)	95.5 (1.0)††**	118.8 (4.2)†††***
Recovery	18	− 77.6 (1.4)	99.4 (1.4)	130.3 (10.4)††***
Control	21	− 77.4 (0.9)	98.2 (1.1)	185.5 (8.7)
2.9×10^{-6}	16	− 72.5 (1.0)*†††	87.9 (1.3)†††***	105.8 (5.3)†††***
Recovery	12	− 76.8 (1.6)	90.9 (2.0)†**	116.0 (14.5)††**
(B) *Purkinje fibres*				
Control	27	− 77.7 (0.9)	103.2 (1.6)	355.3 (15.0)
2.9×10^{-7}	23	− 78.9 (1.1)	104.7 (1.8)	303.5 (15.7)†*
Control	19	− 77.1 (1.0)	100.5 (1.6)	321.3 (15.1)
8.7×10^{-7}	15	− 73.5 (0.9)†	97.8 (1.5)	236.3 (14.5)†††***
Recovery	21	− 75.8 (1.2)	100.6 (1.6)†*	255.4 (15.8)††**

Values are means ± (s.e.mean).
Statistical significance of differences: †$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$, data from all experiments treated as a single population; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, after elimination of between-animal variation (see Methods).

Table 3 Effects on atrial repolarization: times (ms) from action potential peak to 50% (APD_{50}) and 90% (APD_{90}) repolarization

Aprindine						
Concentration ($mol\,l^{-1}$)		0	1.6×10^{-6}	3.2×10^{-6}	6.4×10^{-6}	0 (90 min. recovery)
	n	51	36	39	27	23
APD_{50}		39.8 (0.8)	36.7† (1.0)	35.7††† (0.8)**	37.6 (1.0)*	36.0†† (0.9)
APD_{90}		67.1 (0.8)	67.0 (1.1)	67.3 (1.0)	72.4††† (1.3)	70.9† (1.2)
Indecainide						
Concentration ($mol\,l^{-}$)		0	8.7×10^{-8}	2.9×10^{-7}	8.7×10^{-7}	0 (90 min recovery)
	n	24	24	27	22	20
APD_{50}		33.5 (1.2)	29.2 (1.1)*	28.1† (1.1)**	28.3 (1.0)***	29.9 (1.7)***
APD_{90}		63.0 (2.4)	56.9 (2.1)*	55.4† (1.8)	56.1 (1.4)**	56.5 (1.2)**

Value are means ± (s.e.mean).
Statistical significance of differences as for Table 2.

frequency-dependence would be of little value. At cardiac frequencies compatible with life, it was clear that there could be no recovery during diastole from the effect on MRD of indecainide at a given maintained concentration.

2. Antagonism to adrenoceptor stimulation (Class 2 action)

Dose-response curves for the chronotropic and inotropic responses to isoprenaline of isolated atria were plotted before and during exposure to various concentrations of indecainide, but even the concentration of $2.9 \times 10^{-6}\,mol\,l^{-1}$ (which reduced MRD by 36.2%) had no effect on the responses to isoprenaline, and the results have not, therefore, been presented.

3. Effects on repolarization (Class 3 action)

In the guinea-pig Verdonck *et al.* (1974) had observed that the APD 'of atrial fibres was not significantly altered'. In the rabbit atrium, in contrast, our results, presented in Table 3, demonstrate a significant shortening by aprindine of APD_{50} but no significant effect on APD_{90}. Indecainide produced a significant shortening of both APD_{50} and APD_{90}, and no significant recovery was seen after 90 min washing in drug-free solution.

In papillary muscle (Table 4), indecainide lengthened APD_{50} and APD_{90} at lower concentrations (2.9 and $8.7 \times 10^{-7}\,mol\,l^{-1}$): at the highest concentration used ($2.9 \times 10^{-6}\,mol\,l^{-1}$), a lengthening of APD_{50} was seen, but the effect on APD_{90} was not significant. In Purkinje cells the significant shortening of APD_{50} and APD_{90} by indecainide is comparable with the reported shortening of APD in guinea-pig Purkinje cells by aprindine (Verdonck *et al.*, 1974).

Refractory period Isolated atria were paced at 2.6 Hz, by twice-threshold stimuli, and the effective refractory period (ERP) was measured by a premature stimulus interpolated after every fifth pacing stimulus. Aprindine in concentrations of 1.6, 3.2 and $6.4 \times 10^{-6}\,mol\,l^{-1}$ increased ERP from a control of 59.0 ± 1.9 ms in a dose-related manner by 9.3, 22.5 ($P < 0.05$) and 58.5% ($P < 0.05$) respectively. There was no recovery during washing for 90 min. In contrast, indecainide had no significant effect on ERP measured by programmed stimulation, the respective values being 68.8 ± 8.0 and 71.6 ± 4.7 ms in the control and $8.7 \times 10^{-7}\,mol\,l^{-1}$ indecainide solutions respectively (means ± s.e.mean of 5 preparations). This is consistent with the classification of indecainide as a group 1c agent.

4. Effects associated with restriction of calcium current (Class 4)

The relation between the extracellular calcium concentration, $[Ca]_o$, and the tension developed by isolated atria was plotted before and during exposure to indecainide (Figure 2). Indecainide depressed the log

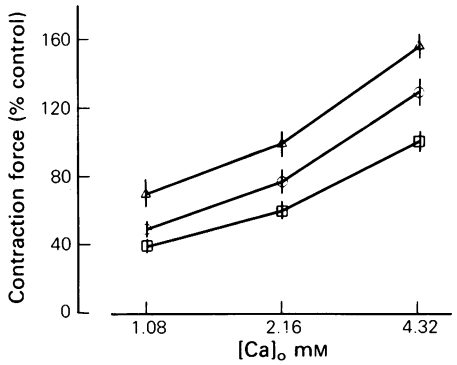

Figure 2 Relation between developed tension and extracellular calcium concentration $[Ca]_o$ before and after esposure to indecainide 2.9×10^{-7} and 2.9×10^{-6} mol l^{-1}. Ordinate scale: force as % of initial control. The mean initial force of contraction was 1.56 g. Abscissa scale: $[Ca]_o$on logarithmic scale

$[Ca]_o$/contraction curve in a concentration-related manner, and in this respect was comparable in potency to verapamil on a molar basis (Salako *et al.*, 1976). By contrast, the effects of indecainide on sinus frequency were not significant: the mean control frequency of 2.14 ± 0.21 Hz was changed to 1.97 ± 0.25 and 2.04 ± 0.28 Hz at 2.9 and 8.7×10^{-7} mol l^{-1} indecainide, respectively ($n = 5$). Aprindine, however, did cause a significant bradycardia, the control frequency of 2.0 ± 0.05 Hz falling by 5.5, 12.5 and 20.0% at the three concentrations shown in Table 1 ($n = 4$: $P < 0.05$ in each case).

5. Effects of hypoxia

Aprindine, which alone caused a shortening of APD (Table 3), paradoxically reduced the shortening of APD induced by hypoxia, especially of APD_{50}, i.e. the plateau was better maintained. Indecainide had no significant effect on hypoxic APD shortening (Figure 3).

The effects of both aprindine and indecainide on MRD (Figure 4a) were similar in hypoxic and in normoxic muscle. The effect of aprindine on conduction velocity was augmented by hypoxia, but indecainide surprisingly increased conduction velocity to values greater than those observed in the hypoxic controls, implying a reduction in cell-to-cell resistance which should, in theory, have an antiarrhythmic effect (Vaughan Williams, 1980).

Discussion

In recent years, antiarrhythmic drugs that were known to have in common the property of restricting fast depolarizing (sodium) current have come to be divided into three groups. The earliest antiarrhythmic agents, including quinidine, procainamide and disopyramide, were known to increase refractory period, and to widen QRS in the human electrocardiogram. Another group of drugs introduced later, including lignocaine, mexiletine and tocainide, also prolonged ERP, but did not widen QRS or alter H–V conduction time in sinus rhythm. They were designated class 1(b), while the earlier group became class 1(a). A third, and more

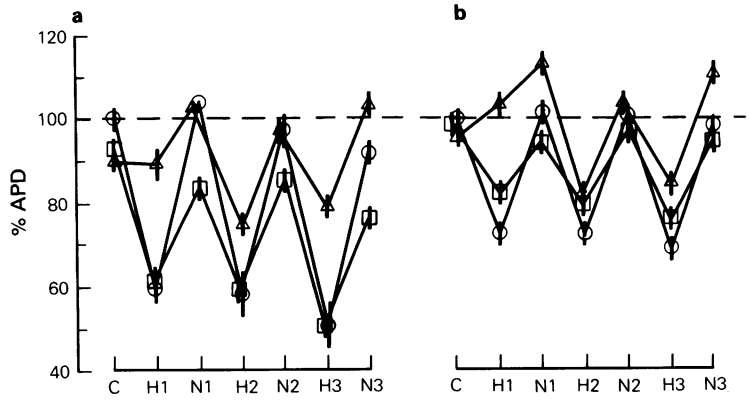

Figure 3 Effects of indecainide on action potential duration from the peak to (a) 50% (APD_{50}) and (b) 90% (APD_{90}) repolarization. C, control before exposure to hypoxia; H1, H2 and H3, successive 15 min periods of hypoxia, N1, N2 and N3, intervening 25 min periods of normoxia. (○): Drug-free controls; (□): in the presence of indecainide 2.29×10^{-7} mol l^{-1}; (△): in the presence of aprindine 3.2×10^{-6} mol l^{-1}. Ordinate scale: APD expressed as % of value before exposure to hypoxia.

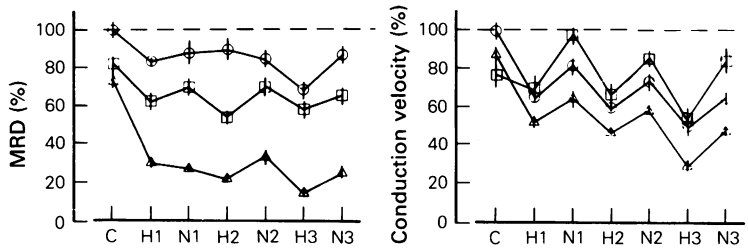

Figure 4 Effects of hypoxia on MRD and conduction velocity. Symbols as for Figure 3. Ordinate scale: MRD and conduction velocity expressed as % of value observed in normoxic drug-free controls.

recent, group of drugs did widen QRS even in sinus rhythm, and prolonged H–V conduction time but had little effect on ERP measured by programmed stimulation. These compounds, including flecainide, lorcainide, encainide and propafenone have been designated class 1(c) (Vaughan Williams, 1984a,b for review).

An electrophysiological explanation for this grouping has been provided on the basis of an analysis of the frequency-dependence of the depression of fast inward current (Campbell & Vaughan Williams, 1983; Campbell, 1983). In studies on isolated ventricular muscle it was shown that drugs of class 1(b) produced, after the onset of stimulation, a progressive reduction of MRD towards a stable level significantly below that seen in the absence of the drug: when stimulation was stopped, and restarted after an interval, MRD rapidly recovered as the pauses lengthened, to reach control values in spite of the continued presence of the drug. Class 1(c) drugs showed much slower onset and offset of effects, while class 1(a) compounds were intermediate in their kinetics. It was concluded that class 1(b) drugs became attached to sodium channels very rapidly after depolarization, and delayed recovery from inactivation after repolarization. Thus few channels were available at the beginning of diastole so that ERP was prolonged. The drugs were swiftly detached from sodium channels at the resting potential so that nearly all of the channels were again available by the end of diastole, with the result that conduction was not delayed, and H–V conduction time and QRS were normal in sinus rhythm. The 1(c) drugs, in contrast, were attached much more slowly to the depolarized channels so that a steady state block was achieved only after many successive action potentials. Recovery was also extremely slow so that hardly any channels with drug attached were released from their inactivated

Table 4 The effects of indecainide on ventricular repolarization times

Concentration (mol l^{-1})	*n*	APD_{50} (ms)	APD_{90} (ms)
(A) *Papillary muscle*			
Control	52	69.8 (1.7)	93.9 (1.7)
2.9×10^{-7}	46	75.0 (2.2)***	99.1 (2.0)†***
Control	44	69.8 (1.9)	93.4 (1.9)
8.7×10^{-7}	30	73.3 (3.4)***	96.8 (3.0)***
Recovery	18	69.5 (1.8)	98.9 (2.5)***
Control	21	81.1 (1.6)	104.9 (1.5)
2.9×10^{-6}	16	87.2 (1.1)††**	107.9 (0.7)
Recovery	12	92.3 (1.9)	115.1 (2.7)*
(B) *Purkinje fibres*			
Control	27	106.4 (3.3)	142.9 (4.3)
2.8×10^{-7}	23	90.8 (3.2)††***	132.5 (4.9)***
Control	19	100.1 (3.7)	136.0 (5.4)
8.7×10^{-7}	15	81.6 (3.9)***	120.3 (5.4)***
Recovery	21	89.6 (4.6)*	126.5 (4.0)*

Values are mean ± (s.e.mean).
Statistical significance of differences as for Table 2.
n = number of fibres from 5 experiments.

state during diastole: H–V conduction was thus delayed and QRS widened. The remaining channels, without drug attached, would be normal, and so would recover rapidly from inactivation after repolarization, which explains why ERP was unaffected.

Indecainide is classified as a class 1(c) compound, because ERP was unchanged, and the onset and offset of its depression of MRD in papillary muscle was extremely slow. In a recent study (Steinberg & Wiest, 1984) the time constant of recovery of MRD in Purkinje fibres in the presence of indecainide after interruption of stimulation was found to be over 50 s.

Class 1 drugs also differ from each other in properties unconnected with their action on sodium channels. Quinidine lengthens APD at high concentrations by a process involving restriction of outward potassium current (Colatsky, 1982). The group 1(b) drugs all shorten APD, especially in the ventricular preterminal Purkinje cells, though opinions have differed concerning the reason for this. Arnsdorf & Bigger (1972) concluded that lignocaine increased potassium permeability, but Carmeliet & Saikawa (1982) and Colatsky (1982) showed that APD shortening by lignocaine in sheep and rabbit Purkinje cells respectively was due to abolition of a tetrodotoxin sensitive sodium current which normally persisted during the plateau.

The shortening of APD by aprindine in atrium, Purkinje cells and ventricle, and by indecainide in atrium and Purkinje cells, might therefore be attributed, at least in part, to blockade of plateau sodium current. Indecainide, which prolonged APD in the ventricle, might have had an additional effect in reducing outward potassium current, like quinidine. If so, in the Purkinje cells, with a higher density of plateau sodium current, the APD-shortening effect of indecainide would have predominated (though still being smaller than that caused by aprindine), whereas in the ventricle the effect on potassium channels would have been more prominent, the net result being a lengthening of APD.

An interesting finding was that indecainide depressed MRD more in atrial muscle at a given concentration than in Purkinje cells. MRD is usually depressed by class 1 drugs to a greater extent in Purkinje cells than in myocardial cells (Millar & Vaughan Williams, 1983), as reported previously for aprindine (Carmeliet & Verdonck, 1974). This effect might have been attributed to a greater density of sodium channels in Purkinje tissue: if so, all class 1 drugs should be more effective in Purkinje cells, but our results with indecainide invalidate this explanation.

The second or slow inward current (i_{SI}) has been said to be responsible both for the initiation of contraction in myocardial cells and for the action potential upstroke in A–V nodal and sinus nodal cells. For example, 'a slow influx of calcium ions . . . acts as the decisive link in excitation-contraction coupling' (Fleckenstein, 1983); 'the slow inward current (i_{SI}) is the only component of the action potential upstroke in some SA node cells' (Brown, 1982). Indecainide, unlike aprindine, had no significant effect on sinus node frequency, from which it might be concluded that it did not restrict i_{SI} in the sinus node. Indecainide did, however, depress contractions in a concentration-related manner in solutions containing normal, half-normal and twice-normal calcium, and in this respect was equal to verapamil in potency, although this does not indicate, of course, that the mechanism of the negatively inotropic action of the two drugs was the same. The negatively inotropic effect, in the absence of any action on the sinus node, contrasts with previous evidence obtained with propafenone and medroxalol (Dukes & Vaughan Williams, 1984a,b) both of which caused bradycardia and reduced MRD in the sino-atrial node at concentrations which had no effect on contractions.

In conclusion, indecainide is about ten times more potent than aprindine as a class 1 antiarrhythmic drug, and belongs to the subgroup (c). In addition, indecainide prolonged APD in the ventricle. It might be preferentially effective in arrhythmias of atrial origin because it depressed MRD to a greater extent in atrial muscle than elsewhere but the very persistent action of indecainide would entail a risk of irreversible conduction failure on overdosage.

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