Effects of hyperkalaemia on the depression of maximum rate of depolarization by class I antiarrhythmic agents in guinea-pig myocardium

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1 Standard microelectrode methods were used to record intracellular action potentials from strips of guinea-pig right ventricular myocardium superfused with either standard physiological saline ($[K^+] = 5.6$ mM) or the same solution modified to contain $[K^+] = 11.2$ mM.

2 The effects on action potential parameters of three therapeutic concentrations of mexiletine, quinidine and disopyramide were studied under both conditions at four different drive rates (interstimulus intervals = 2400, 1200, 600 and 300 ms).

3 Hyperkalaemia in the absence of drugs produced reductions in resting potential (-86.7 ± 2.5 mV to -71.8 ± 3.7 mV; $n = 30$; $P < 0.001$), maximum rate of depolarization (300 ± 46.5 V s $^{-1}$ to 205.6 ± 37.6 V s $^{-1}$; $P < 0.0001$), and action potential duration (205 ± 26 ms to 188 ± 32 ms; $P < 0.05$).

4 All three drugs produced increased depression of maximum rate of depolarization in hyperkalaemia compared to control conditions, but at all three concentrations this enhancement of effect was greater for mexiletine than for quinidine, with disopyramide exhibiting intermediate behaviour.

5 Mexiletine behaved very similarly to therapeutic concentrations of lignocaine as described in previous reports from this laboratory.

6 Quinidine behaved very similarly to Class Ic agents.

7 It is concluded that mexiletine demonstrated significantly greater selectivity for depolarized myocardium than quinidine and that this may have implications in terms of proarrhythmic potential.

8 Disopyramide exhibited intermediate selectivity for depolarized myocardium between mexiletine and quinidine.

Keywords: Quinidine; disopyramide; flecainide; mexiletine; lignocaine; hyperkalaemia; depolarization; myocardium; sodium channel; Class I antiarrhythmic agents; antiarrhythmic drugs; cardiac action potential; ischaemia

Introduction

In a recent series of publications we have demonstrated that the Class Ic antiarrhythmic drugs, encainide and flecainide, exhibit significantly less enhancement of their blockade of the fast inward sodium channel in simulated ischaemic conditions than lignocaine or amiodarone (Campbell & Hemsworth, 1990; Campbell *et al.*, 1991). The greater selectivity for cells subjected to acidosis and hyperkalaemia demonstrated for lignocaine and amiodarone over flecainide and encainide implies that the first two agents may be given in concentrations that markedly depress ischaemic areas of myocardium but have little or no effect on normal tissue. This desirable behaviour seems less likely to be achieved with Class Ic agents such as flecainide and encainide. We hypothesised that this may cast further light on the clinically observed proarrhythmic properties of these latter agents. It was noted during the course of these experiments, in which three of the main components seen in ischaemic myocardium (hyperkalaemia, acidosis and hypoxia), were studied individually, that hypoxia had no effect on drug binding, acidosis had only modest effects and by far the largest contributing factor to the enhanced blockade of the sodium channel by Class I drugs in our model of simulated ischaemia was depolarization subsequent to hyperkalaemia. For this reason, in the experiments to be described below we have studied the effects of this intervention only.

In 1987, Hondeghem suggested that Class I drugs which appear to bind with high affinity to inactivated sodium channels, should be more likely to exhibit such ischaemia-

selective behaviour than drugs which bind preferentially to activated (open) channels. It was this suggestion that led us to compare Class I agents known to bind selectively to the inactivated state of the sodium channel (such as lignocaine and amiodarone), with those which behave predominantly as open channel blockers (flecainide, encainide and other Class Ic agents). Earlier work from this laboratory had already shown that the relative degree of inactivated versus activated sodium channel block of various Class I antiarrhythmic drugs correlated with the kinetics of their interaction with the sodium channel (Campbell, 1983). Thus compounds with fast kinetics (Class Ib agents and amiodarone) have a high affinity for the inactivated state of the sodium channel and appear to demonstrate a great degree of selective depression of ischaemic myocardium, whereas Class Ic agents with slow kinetics demonstrate significantly less selectivity for ischaemic myocardium. The Class Ia antiarrhythmic agents such as quinidine, disopyramide and procainamide have intermediate kinetics of interaction with the sodium channel, and we suggested that they may demonstrate an intermediate affinity for ischaemic myocardium. We therefore set out in the series of experiments to be described below, firstly to confirm that the Class Ib agent, mexiletine, shared the high affinity for ischaemic myocardium we had previously demonstrated for lignocaine and amiodarone, and then to test the hypothesis that Class Ia antiarrhythmic agents would show intermediate degrees of selectivity for ischaemic tissue in our model.

Lignocaine has the practical disadvantage of being useful only as an intravenous infusion. Mexiletine on the other hand is active when given orally and has virtually identical cellular electrophysiological properties to lignocaine. For this reason it is often used by clinicians to treat arrhythmias for

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which intravenous lignocaine has already been successful. Ischaemia-selective behaviour would only be of clinical importance if demonstrated at therapeutically relevant concentrations. The therapeutic range for mexiletine is approximately 3.5 to 10 μM (Campbell *et al.*, 1978) and we therefore studied this agent at concentrations of 5, 10 and 20 μM , in a preparation identical to that used in the previous publications from this laboratory.

The accepted therapeutic ranges of plasma concentration for quinidine and disopyramide are approximately 5 to 15 μM (Hoffmann *et al.*, 1975) and 8 to 22 μM (Niarchos, 1976) respectively. To provide adequate coverage of this range, we studied both agents at the same concentrations as used for mexiletine, namely 5, 10 and 20 μM .

Methods

Guinea-pigs of either sex weighing 300 to 700 g were decapitated and their hearts quickly removed. Strips (approximately 5 mm $\times$ 3 mm $\times$ 1 mm) were cut from the right ventricular free wall and pinned to the base of a bath (volume 0.5 ml). The tissue was superfused at 3 ml min⁻¹ with 'control' solution, gassed with 95% O₂ and 5% CO₂ and maintained at 36 $\pm$ 0.2°C by a Peltier element. The composition of this standard superfusate was as follows (mM): NaCl 125, KCl 5.6, CaCl₂ 2.16, NaHCO₃ 25, MgCl₂ 1.0, NaH₂PO₄ 0.44 and glucose 11. The 'hyperkalaemic' superfusate was identical to this except that the KCl concentration was doubled to 11.2 mM.

Preparations were allowed to equilibrate in control superfusate for at least 1 h. When required by the protocol, they were driven by bipolar platinum electrodes providing rectangular pulses of 2 ms duration and sufficient amplitude to limit variations in latency between stimulus and action potential upstroke to less than 2 ms.

Action potentials were recorded from cells on the surface of the preparation with conventional glass microelectrodes filled with 3 M KCl coupled to a high input impedance d.c. amplifier with negative capacitance compensation (either WPI 750 or Neurolog NL 102). To study rate-dependent effects, the preparations were driven at four different interstimulus intervals (ISI) ranging from 300 to 2400 ms, for periods long enough to achieve a stable level of $\dot{V}_{\text{max}}$. In the absence of drug, stimulation led to minor, rate-dependent falls in $\dot{V}_{\text{max}}$ with rapid equilibration at a new, reduced value of $\dot{V}_{\text{max}}$ which then remained constant during continued stimulation at the same rate. In the presence of all three drugs, there were more marked, rate-dependent reductions in $\dot{V}_{\text{max}}$. All such reductions have been expressed as percentage change from the value of $\dot{V}_{\text{max}}$ recorded for the first action potential after prolonged quiescence in drug-free superfusate. All experiments involved continuous impalements of single cells.

Action potentials were monitored on an oscilloscope, and sampled at 20 kHz with a DT 2801-A analog-digital converter, fitted to a IBM personal computer. Analysis was performed by use of software developed in the department (the maximum rate of depolarization being calculated by simple differencing of adjacent samples).

Lignocaine hydrochloride and quinidine sulphate were purchased commercially (Sigma, St. Louis, MO, U.S.A.). Mexiletine was kindly donated by Boehringer Ingelheim and disopyramide by Roussel. All drugs were made as stock solutions in distilled water and then diluted freshly in the relevant superfusate. During repetitions of experiments, the sequence of exposure to the various solutions under study was randomized where possible to minimize any order effects.

All data are expressed as mean $\pm$ standard deviation. One way analysis of variance (ANOVA), was used to test for the significance of drug effect on $\dot{V}_{\text{max}}$, followed in some cases by Student's *t* tests with the Bonferroni correction for multiple comparisons, to define differences between specific pairs of

samples. Two-way ANOVA was used to compare the effects of different drugs across a range of stimulation rates.

All the experiments described have been approved by the Committee for the Use of Animals in Research and Teaching, University of New South Wales, and the Animal Ethics Committee, St. Vincent's Hospital.

Results

Effects of hyperkalaemia in the absence of drugs

The effects on action potential parameters of superfusion for 20 min with high K⁺ solution (K⁺ = 11.2 mM versus 5.6 mM in control), were very similar to those previously reported by us for this preparation (Campbell *et al.*, 1991). The resting membrane potential fell from -86.7 ± 2.5 mV to -71.8 ± 3.7 mV ($n = 30$; $P < 0.001$). There was a corresponding reduction in action potential amplitude from 123.2 ± 4.3 mV to 106.4 ± 4.4 mV ($P < 0.001$), and action potential duration at 90% of repolarization (APD₉₀), fell from 205 ± 26 ms to 188 ± 32 ms ($P < 0.05$). The maximum rate of depolarization ($\dot{V}_{\text{max}}$) fell from 300 ± 46.5 V s⁻¹ to 205.6 ± 37.6 V s⁻¹ ($P < 0.0001$). These data are those recorded at an interstimulus interval of 1200 ms. Qualitatively similar results were obtained at other rates. All of these effects were fully reversible after 15 to 20 min washing in control solution.

Modulation of drug effects by hyperkalaemia

No drug in any of the three concentrations used has a statistically significant effect on resting potential or action potential amplitude in control superfusate. This was also true in the hyperkalaemic superfusate. There was a non-significant trend for mexiletine to shorten action potential duration (APD₉₀) in a dose-dependent manner. At ISI = 1200 for example, APD₉₀ in drug-free solution was 223.9 ± 13.8 ms and this fell in a concentration-dependent manner to 194.3 ± 18.3 ms at mexiletine 20 μM . Disopyramide and quinidine on the other hand showed a trend to slightly increase action potential duration, which was more evident at slower stimulation rates and lower concentration-ranges. This trend reached significance only for 5 μM of disopyramide at 1200 and 2400 ms ISI and represented a prolongation of less than 10% in APD.

All drugs produced highly significant, partially or completely reversible reductions in $\dot{V}_{\text{max}}$ in some or all of the four ISIs investigated (2400, 1200, 600 and 300 ms). This was true in both superfusates. Because of the wide between-cell variations in control $\dot{V}_{\text{max}}$ values, this effect has been expressed as total percentage depression of $\dot{V}_{\text{max}}$ below control values, recorded in previously quiescent tissue (the same parameter used in our previous reports). At each ISI, stimulation was continued until $\dot{V}_{\text{max}}$ achieved a stable level. These data are presented in Table 1.

Mexiletine As noted above, superfusion with high K⁺, drug-free solution produced large rate-dependent reductions in $\dot{V}_{\text{max}}$. The dose- and rate-dependent reductions of $\dot{V}_{\text{max}}$ produced by each of the drugs was also enhanced by changing from normal K⁺ to high K⁺ superfusate (Table 1). In this regard, as can be seen from Figure 1, mexiletine behaved very similarly to lignocaine at each of the three concentrations used. It can be seen that in the lower two concentrations for each drug, suppression of $\dot{V}_{\text{max}}$ at each ISI in both normal and high K⁺ superfusate was virtually identical. At the highest concentration (20 μM mexiletine and 30 μM lignocaine), mexiletine produced greater depression of $\dot{V}_{\text{max}}$ than did lignocaine ($P < 0.001$), but this difference between the drugs was maintained on changing to high K⁺ solution.

Table 1 Percentage reduction of V_{max} by four drugs at four different stimulation rates in normal and high K⁺ solutions

Drug	ISI =	Normal K ⁺ superfusate			High K ⁺ superfusate		
		300	600	1200	300	600	1200
Drug-free (n = 30)		7.2 ± 2.6	4.0 ± 2.1	3.5 ± 1.6	44.6 ± 14.0	37.3 ± 12.1	34.4 ± 11.9
Lignocaine 7.5 µM (n = 13)		27.2 ± 7.9***	13.0 ± 6.0**	9.7 ± 4.9*	69.0 ± 15.9***	53.6 ± 9.5**	46.6 ± 9.2*
Lignocaine 15 µM (n = 12)		32.3 ± 8.3***	16.8 ± 5.1***	11.9 ± 6.7**	7.39 ± 11.8***	61.4 ± 15.2***	52.0 ± 10.9***
Lignocaine 30 µM (n = 11)		42.5 ± 9.6***	20.9 ± 6.5***	14.9 ± 6.6***	86.9 ± 13.1***	72.0 ± 16.2***	63.6 ± 15.0***
Mexiletine 5 µM (n = 5)		29.9 ± 4.9***	18.6 ± 4.3***	13.4 ± 5.1*	66.7 ± 11.0*	56.1 ± 13.0*	50.0 ± 14.3
Mexiletine 10 µM (n = 6)		36.8 ± 6.9***	22.8 ± 4.7***	16.5 ± 5.8***	84.1 ± 13.0***	67.1 ± 18.0***	52.9 ± 9.9*
Mexiletine 20 µM (n = 5)		55.6 ± 8.6***	33.9 ± 7.5***	23.2 ± 8.3***	92.4 ± 11.0***	79.0 ± 13.8***	72.9 ± 17.0***
Quinidine 5 µM (n = 6)		27.9 ± 15.9***	20.3 ± 13.9***	14.3 ± 11.2**	50.2 ± 9.3	46.4 ± 11.5	37.6 ± 13.4
Quinidine 10 µM (n = 5)		44.9 ± 10.8***	35.8 ± 11.2***	28.2 ± 7.7***	72.8 ± 18.3**	56.0 ± 13.0	52.4 ± 13.1*
Quinidine 20 µM (n = 5)		52.3 ± 16.4***	46.9 ± 16.5***	40.6 ± 17.0***	82.3 ± 18.4***	67.5 ± 8.7***	59.3 ± 9.3***
Disopyramide 5 µM (n = 6)		25.5 ± 8.3***	16.3 ± 3.5**	13.8 ± 3.2**	61.5 ± 10.3	53.9 ± 10.6	48.4 ± 10.2
Disopyramide 10 µM (n = 5)		36.1 ± 9.6***	26.6 ± 9.0***	21.5 ± 3.2***	67.1 ± 11.8*	59.6 ± 8.0*	50.8 ± 7.2
Disopyramide 20 µM (n = 5)		38.5 ± 4.8***	28.7 ± 4.9***	24.2 ± 3.3***	90.5 ± 9.3***	67.8 ± 12.2***	59.7 ± 12.2**

*P<0.05; **P<0.01; ***P<0.001, significance of difference from drug-free superfusate (one-way ANOVA with Bonferroni correction). Data points are percentage reductions in V_{max} during prolonged stimulation compared to maximum V_{max} recorded following prolonged quiescence in drug-free superfusate. ISI = interstimulus interval.

Figure 1 Relationship between interstimulus interval and percentage reduction in $\dot{V}_{\max}$ under normal ($K^+ = 5.6$ mM; open symbols) and hyperkalaemic ($K^+ = 11.2$ mM; closed symbols) conditions in the presence of lignocaine ($\circ, \bullet$) and mexiletine ($\Delta, \blacktriangle$). Concentrations of each agent used are: (a) lignocaine $30 \mu\text{M}$ and mexiletine $20 \mu\text{M}$; (b) lignocaine $15 \mu\text{M}$ and mexiletine $10 \mu\text{M}$; (c) lignocaine $7.5 \mu\text{M}$ and mexiletine $5 \mu\text{M}$. At each concentration range in the normal K^+ superfusate, lignocaine tends to produce slightly less depression of $\dot{V}_{\max}$ than does mexiletine. The main point of the figure is that the depression of $\dot{V}_{\max}$ by both agents is markedly and approximately equally enhanced in the presence of high K^+ superfusate.

Quinidine and disopyramide

Quinidine contrasts with mexiletine and lignocaine in that its depression of $\dot{V}_{\max}$ shows significantly less enhancement in the presence of hyperkalaemia than was seen with the Class Ib agents (Table 1). Thus in normal K^+ superfusate, at each of the three concentrations used ($5 \mu\text{M}$, $10 \mu\text{M}$ and $20 \mu\text{M}$), quinidine produced the same or more depression of $\dot{V}_{\max}$ than did the corresponding dose of mexiletine at any given ISI. The situation is quite the reverse when high K^+ superfusate is substituted. Figure 2 illustrates this for the low and high concentrations of these agents.

Similar though less striking contrasts were seen between disopyramide and mexiletine, particularly in the higher concentration-ranges (Figure 3). Thus disopyramide $5 \mu\text{M}$ and mexiletine $5 \mu\text{M}$ behaved rather similarly, both in normal K^+ and high K^+ superfusate, but a lower selectivity of disopyramide for depolarized tissue was evident at higher concentrations, so that at $20 \mu\text{M}$, disopyramide and mexiletine had similar effects in low K^+ superfusate ($P = 0.06$), but except at the faster rate, mexiletine $20 \mu\text{M}$ exhibited significantly more

Figure 2 Format as for Figure 1, comparing mexiletine ($\Delta, \blacktriangle$) and quinidine ($\diamond, \blacklozenge$) at equimolar concentrations of $5 \mu\text{M}$ (a) and $20 \mu\text{M}$ (b). At $5 \mu\text{M}$ in control superfusate, quinidine and mexiletine are approximately equipotent. In hyperkalaemic superfusate, the depression of $\dot{V}_{\max}$ by mexiletine is significantly greater ($P = 0.002$; two-way ANOVA) than that of quinidine. In high concentrations the disparity is more marked. In control superfusate, mexiletine has significantly less effect on $\dot{V}_{\max}$ than does quinidine ($P = 0.02$). In hyperkalaemic superfusate, the situation is reversed with mexiletine having significantly more effect than does quinidine ($P = 0.008$).

depression of $\dot{V}_{\max}$ than did disopyramide $20 \mu\text{M}$ in high K^+ superfusate ($P = 0.02$ overall; Figure 3).

The fact that the behaviour of disopyramide in this preparation is intermediate between quinidine and mexiletine is further illustrated by Figure 4. It can be seen that at both the low and high ends of the concentration-ranges, disopyramide exhibited greater enhancement of its depression of $\dot{V}_{\max}$ in the presence of high K^+ superfusate than did quinidine. Figure 5 provides further information on this point, using previously published data from this laboratory studying the effects of $1 \mu\text{M}$ flecainide in the same preparation ($n = 5$; Campbell *et al.*, 1991). It can be seen that while $5 \mu\text{M}$ disopyramide exhibited significantly more selectivity for depolarized myocardium than did $1 \mu\text{M}$ flecainide, $5 \mu\text{M}$ quinidine behaved in a very similar fashion to the Class Ic agent, flecainide. Thus disopyramide behaved in an intermediate fashion in terms of its selectivity for depolarized myocardium, being significantly less selective than the Class Ib agent, mexiletine and significantly more selective than the Class Ic agent, flecainide. Quinidine however, behaves in a manner essentially similar to that previously described for Class Ic agents.

Discussion

The potential for antiarrhythmic agents to worsen or actually provoke arrhythmias has recently been brought into sharp

Figure 3 Format as for Figure 2, comparing mexiletine (Δ , $\blacktriangle$) and disopyramide ($\square$, $\blacksquare$) at concentrations of $5\ \mu\text{M}$ (a) and $20\ \mu\text{M}$ (b). At $5\ \mu\text{M}$, disopyramide and mexiletine behave essentially identically in both control superfusate and hyperkalaemic superfusate ($P = 0.2$ and 0.4 respectively). At $20\ \mu\text{M}$ however, while the two drugs remain essentially equipotent in terms of their depression of $\dot{V}_{\text{max}}$ at $\text{K}^+ = 5.6\ \text{mM}$ ($P = 0.07$), mexiletine demonstrates significantly greater depression of $\dot{V}_{\text{max}}$ in hyperkalaemic superfusate than does disopyramide ($P = 0.02$).

focus by the results of the Cardiac Arrhythmia Suppression Trial (CAST; Echt *et al.*, 1991), and by meta-analyses of trials of the use of quinidine in atrial fibrillation and ventricular arrhythmias (Coplen *et al.*, 1990; Morganroth & Goin, 1991). It seems likely that one of the major mechanisms of proarrhythmia is facilitation by Class I antiarrhythmic drugs of actual or potential re-entrant circuits due to a critical reduction of conduction velocity within these areas of myocardium (Campbell, 1990). It seems intuitively likely that the greater the degree of myocardial damage, either permanent (due to ischaemic heart disease, cardiomyopathy etc.) or transient (due to ischaemia), the greater the likelihood that the electrophysiological actions of an antiarrhythmic agent might 'uncover' or facilitate a potential substrate for re-entry. It is certainly well documented that agents such as flecainide produce a higher incidence of proarrhythmic effects in patients with more severe ventricular dysfunction (Morganroth & Horowitz, 1984; Morganroth *et al.*, 1986a; Morganroth, 1987). Similar, though less striking trends have been reported for encainide and quinidine (Morganroth, 1986b; 1987; Denes *et al.*, 1981).

The most likely explanation for this is the well known interaction between Class I antiarrhythmic drugs and depolarized myocardium (Hondeghe, 1987). An almost universal response of myocardium to an acute or chronic insult such as ischaemia, is partial depolarization. This in turn will tend to enhance the conduction slowing effects of any antiarrhythmic agents to which the myocardium may happen to be

Figure 4 Format as for Figures 2 and 3, comparing quinidine ($\diamond$, $\blacklozenge$) and disopyramide ($\square$, $\blacksquare$) at $5\ \mu\text{M}$ (a) and $20\ \mu\text{M}$ (b). The depression of $\dot{V}_{\text{max}}$ by disopyramide is enhanced to a significantly greater extent than that seen for quinidine in both concentrations. At $5\ \mu\text{M}$, the two drugs are equipotent in control solution ($P = 0.5$) and disopyramide is significantly more depressant than quinidine in hyperkalaemic superfusate ($P = 0.004$). At $20\ \mu\text{M}$, quinidine depresses $\dot{V}_{\text{max}}$ significantly more than does disopyramide in the control superfusate ($P < 0.001$), but the two agents produce equal depression in the hyperkalaemic superfusate ($P = 0.7$).

exposed at the time. One of the working hypotheses behind the present experiments was the proposition that Class I drugs which possess more marked selectivity for partially depolarized cells could be given in concentrations that markedly depress ischaemic tissues (thus maximizing the likelihood of abolishing the focus of the index arrhythmia) but which have little or no effect on normal myocardium (thus minimizing the propensity for producing new arrhythmogenic sites within the heart). Widespread, non-selective depression of conduction velocity is well known to enhance the likelihood of re-entrant arrhythmias (Hondeghe, 1987; Campbell, 1990), and indeed very recent laboratory studies have confirmed the ability of flecainide to produce 'fibrillation' in normal, non-ischaemic myocardium *in vitro* (Brugada *et al.*, 1991).

It follows from this argument therefore, that the proarrhythmic propensity of a Class I agent might be expected to correlate with the degree of selectivity it possesses for depressing ischaemic or depolarized myocardium, relative to normal fully polarized cells (which in turn has been shown to correlate with affinity for the inactivated state of the sodium channel: Hondeghe, 1987; Campbell, 1983). The experiments previously reported by us (Campbell & Hemsworth, 1990; Campbell *et al.*, 1991), have already confirmed significantly greater selectivity for ischaemic tissue for amiodarone and lignocaine over the Class Ic agents, flecainide and encainide. The data presented above confirm that the Class Ib drugs, mexiletine and lignocaine, exhibit similar degrees of

Figure 5 Format as for Figures 2 to 4, comparing quinidine 5 μM ($\blacklozenge$, $\diamond$) with flecainide 1 μM ($\circ$, $\bullet$; a) and disopyramide 5 μM ($\square$, $\blacksquare$) with flecainide 1 μM ($\circ$, $\bullet$; b). Quinidine and flecainide exhibit very similar degrees of depression of $\dot{V}_{\text{max}}$ in both control and high K^+ solution ($P = 0.3$ and 0.7 respectively), whereas disopyramide shows significantly greater selectivity for depolarized myocardium than does flecainide ($P = 0.4$ in control and 0.006 in high K^+).

selectivity for depolarized cells, and that the Class Ia agents quinidine and disopyramide possess significantly less selectivity. Furthermore, comparison of the present data with experiments on the Class Ic agent, flecainide, previously published from this laboratory, demonstrate that the behaviour of disopyramide is truly intermediate between that of Ib and Ic agents, whereas quinidine behaves essentially the same as the Class Ic agents, demonstrating minimal selectivity for ischaemic myocardium. In the original study comparing nine drugs from each of the three sub-classes of sodium channel blockers in terms of their kinetics of interaction with the sodium channel, the kinetics of the Class I agents were (as noted above), intermediate between those of Class Ib and Class Ic. In addition to this, it was noted that disopyramide had the fastest onset kinetics of all the Class Ia agents and demonstrated the greatest ability to prolong the effective refractory period relative to the action potential duration of the sub-group. This would be consistent with its possessing greater selectivity for depolarized myocardium than quinidine, as was the case in the present study (Campbell, 1983; Vaughan Williams, 1984).

Clinical relevance

Does this correlate with clinically observed incidences of proarrhythmia with the various agents? Hard data on this issue are difficult to find in the literature, largely due to the

scarcity of large-scale studies which compare two or more Class I antiarrhythmic agents 'head-to-head' in terms of their proarrhythmic propensity. There is certainly a widespread perception among cardiologists that the newer Class Ic agents such as flecainide and encainide appear more likely to produce proarrhythmia than Class Ia drugs, and that mexiletine is less prone to proarrhythmic problems than many other Class I compounds (Morganroth, 1992). In support of this, the best data relevant to the present study which compare mexiletine to other agents, come from the Mexiletine-Quinidine Research Group (Morganroth and Mexiletine-Quinidine Research Group, 1987), who studied approximately 500 patients with ventricular ectopic beats and/or ventricular tachycardia, in which the incidence of proarrhythmia was 9% for those patients on quinidine, compared to 5% for patients on mexiletine. The 95% confidence intervals for the mortality risk difference between mexiletine and quinidine ranged from 0 to 40%. In other words, this study fell just short of showing a statistically significant benefit for mexiletine over quinidine in terms of mortality.

The only direct comparison of disopyramide and quinidine available had only 62 patients in each group and focused on efficacy (Arif *et al.*, 1983). The authors reported no mortality from either drug. Certainly the two compounds behave very similarly in the Electrophysiology Laboratory both *in vitro* and *in vivo*, thus adding further support to the hypothesis that their proarrhythmic profiles are not markedly different from each other.

It is more difficult to be certain whether the current perception that Ic agents are more dangerous than quinidine or disopyramide is truly justified. Indeed, if the data presented here are of major relevance to proarrhythmia, one might expect quinidine at least to be comparable to flecainide in this regard, with disopyramide possibly a little safer. Certainly, data from a recent meta-analysis of the use of quinidine for ventricular arrhythmias do not suggest that quinidine is significantly safer than flecainide (Morganroth & Goin, 1991), but the issue here is clouded because quinidine and disopyramide are far more likely than Ib or Ic antiarrhythmic agents to produce early afterdepolarizations and 'torsades de pointes' (Jackman *et al.*, 1988; Campbell, 1990). It thus becomes very difficult to ascertain whether quinidine and disopyramide are less likely than flecainide or encainide to provoke arrhythmias specifically via their effects on conduction, the only mechanism of relevance to the present study. Neither compound was included in the Cardiac Arrhythmia Suppression Trial, and the prospects of a future large-scale trial being organised to answer this question seem rather low. Suffice it to say however, that the data presented above are quite consistent with the hypotheses that proarrhythmia due to facilitation of re-entrant tachycardia is less likely to occur with antiarrhythmic agents that show a high degree of selectivity for partially depolarized myocardium (mexiletine and similar drugs) and more likely to occur with drugs demonstrating intermediate or low degrees of selectivity for such tissue (disopyramide, quinidine and Ic agents respectively).

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