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European Journal of Pharmacology 285 (1995) 229–238

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Lack of selectivity for ventricular and ischaemic tissue limits the antiarrhythmic actions of lidocaine, quinidine and flecainide against ischaemia-induced arrhythmias

T.D. Barrett, E.S. Hayes, M.J.A. Walker *

Department of Pharmacology and Therapeutics, Faculty of Medicine, University of British Columbia, 2176 Health Sciences Mall, Vancouver, B.C., Canada V6T 1Z3

Received 27 February 1995; revised 16 May 1995; accepted 30 June 1995

Abstract

The antiarrhythmic effectiveness, electrocardiographic and haemodynamic properties of three representative class I antiarrhythmics have been investigated in anaesthetized rats. Quinidine, lidocaine and flecainide were chosen as representatives of class Ia, Ib and Ic, respectively. Lidocaine showed the greatest frequency and 'ischaemia' dependency and a high dose provided complete protection against ischaemic arrhythmias induced by coronary artery occlusion. Flecainide showed the least frequency and ischaemia dependency and the least antiarrhythmic effectiveness. Quinidine was only slightly more effective than flecainide. The three drugs were approximately equi-potent in lowering blood pressure which limited the maximum dose that could be tested. The highest dose of lidocaine also caused convulsions in conscious animals. Thus, while lidocaine had selectivity for ischaemic tissue, and for high frequencies, the central nervous system and cardiovascular toxicity limited its usefulness against ischaemia-induced arrhythmias. Quinidine and flecainide's lack of selectivity for ischaemia, and/or high frequencies, probably accounted for their limited antiarrhythmic actions against ischaemia-induced arrhythmias. This study emphasizes that class I drugs can only provide useful protection against ischaemia-induced arrhythmias if they have marked cardiac selectivity as well as selectivity for ischaemic cardiac tissue.

Keywords: Ischemic arrhythmia; Antiarrhythmic, class I; (Selectivity); ECG (electrocardiogram)

1. Introduction

The CAST trial has had a major influence on how the antiarrhythmic actions of currently available class I antiarrhythmics are viewed (Echt et al., 1991). The CAST trial demonstrated that the class I drugs used in that study did not prevent the occurrence of sudden death (Greene et al., 1992). However, while sudden death in the study could have been due to acute myocardial ischaemia, we cannot interpret the findings of the CAST study as indicating that class I drugs cannot protect against ventricular tachyarrhythmias induced by myocardial ischaemia. Similarly, despite the fact that few clinical trials have ever shown beneficial effects on mortality which is attributable to class I antiarrhythmic activity (Roden, 1994) we cannot conclude that such drugs are unable to confer protection against ischaemia-induced arrhythmias. After all, although lidocaine may not reduce mortality it has been shown clinically in the setting of myocardial ischaemia to prevent the occurrence of ventricular fibrillation (Hine et al., 1989).

A number of experimental studies in various species have shown that class I antiarrhythmics protect against ischaemia-induced arrhythmias. However, such protection is incomplete and compromised by excessive toxicity (see review by Botting et al., 1985 for the earlier evidence). The reasons for the limited effectiveness of class I antiarrhythmics is not readily apparent but is possibly multi-factorial in nature. Hondeghem (1991) has argued persuasively that antiarrhythmics have to be pathologically specific before they can provide protection. Thus an ideal antiarrhythmic would be expected to have no effect on normal cardiac tissue at normal

* Corresponding author. Tel. +1 604 822 9531, fax +1 604 822 9578, e-mail RSDAA@unixg.ubc.ca.

SSDI 0014-2999(95)00406-8

sinus rhythm. Hondeghem (1991) further suggested that drugs with appropriate state-dependent blocking actions would show the required specificity. We have previously suggested that selectivity for ischaemia-induced arrhythmias could be obtained by taking advantage of the conditions which prevail in ischaemic cardiac tissue (Curtis and Walker, 1988b; Abraham et al., 1989).

The failure of many class I drugs to completely prevent ischaemia-induced arrhythmias may be due to a relative lack of the selectivity shown by lidocaine. An alternative explanation for the relative lack of antiarrhythmic efficacy of many class I antiarrhythmics may be an inappropriate pharmacological profile whereby the presence of other pharmacological actions prevents the full expression of an antiarrhythmic action (see review by Roden, 1994). Acute toxicity associated with class I antiarrhythmics includes cardiovascular depression and/or neuronal toxicity (see Roden, 1994). Neuronal (CNS) toxicity is particularly common with class Ib drugs such as lidocaine and mexiletine (Roden, 1994; Lie et al., 1974; Hondeghem, 1991) reflecting a lack of selective blockade of cardiac sodium currents. Cardiovascular depression via actions on the myocardium or vasculature is particularly common with many antiarrhythmics (Bigger and Hoffman, 1990).

In summary, class I drugs may lack efficacy against ischaemia-induced arrhythmias because of one, or a combination, of the following: (1) lack of cardiac selectivity; (2) lack of selectivity for ischaemic tissue; (3) excess of other pharmacological actions. As a test of this hypothesis, we have examined the antiarrhythmic and other actions of three representative class I drugs, quinidine, lidocaine and flecainide. We compared these drugs, both in vivo and in vitro, for cardiovascular and electrophysiological actions especially with respect to effectiveness against ischaemia-induced arrhythmias. The results of this study suggest that, at least in rats, all three drugs lacked sufficient cardiac, and/or ischaemic tissue selectivity, to confer protection against ischaemia-induced arrhythmias in conscious animals.

2. Materials and methods

Cardiovascular, ECG, electrophysiological and antiarrhythmic actions of quinidine, lidocaine and flecainide were studied in vivo and in vitro using male Spraque-Dawley rats of 250–350 g weight. Experiments were performed according to protocols approved by the UBC Animal Care Committee. All three drugs, given as boluses or infusions, were studied in vivo for actions on blood pressure, heart rate and the ECG. Infusion regimens were used to determine the effects of the drugs on responses to electrical stimulation of the left ventricle including electrical induction of ventricular fibrillo-flutter. Studies were also performed in isolated perfused hearts to determine drug effects in the presence of either normal or 'ischaemic' perfusates.

2.1. Intact animals

Rats were anaesthetized with 65 mg kg^{-1} pentobarbital i.p. The jugular vein, carotid artery and trachea were cannulated for injection, blood pressure measurement and artificial ventilation, respectively. Animals were ventilated at a stroke volume of 10 ml kg^{-1}, 60 strokes $minute^{-1}$. A lead II ECG was also recorded. Body temperature was monitored via a rectal thermometer and maintained by means of a heating lamp. Drugs were administered cumulatively according to a random and blind design. For in vivo experiments, a stock solution of lidocaine was made by dissolving it in 10% dimethyl sulphoxide (DMSO), 10% ethanol and 80% distilled water whereas stock solutions of quinidine and flecainide were dissolved in 22% ethanol and 78% distilled water. Appropriate vehicle control groups were included in all experiments.

2.2. Electrical stimulation

In order to stimulate the left ventricle in vivo, two Teflon-coated silver wires were inserted via needles passed through the chest wall into the left ventricle. Using a Grass model SD9 stimulator, threshold current (iT, μA) and pulse width (tT, ms) for induction of extra systoles, maximum following frequency (MFF, Hz), effective refractory period (ERP, ms) and ventricular fibrillo-flutter threshold (VFT, μA) were determined according to methods previously described (Walker and Beatch, 1988). Ventricular fibrillo-flutter threshold is defined by a characteristic high frequency ECG pattern with components resembling fibrillation and flutter (high rate tachycardia) and accompanied by a marked fall in blood pressure.

2.3. Isolated hearts

The isolated heart apparatus described by Curtis et al. (1986) was employed. Rats were anaesthetized with 70 mg kg^{-1} pentobarbital and given 1000 units of heparin i.p. prior to excision of the heart. Excised hearts were removed and immediately perfused with ice cold Krebs/1,4-piperazine bissulphonic acid (Krebs/Pipes) perfusate (pH 7.4) before being placed on a special Langendorff apparatus and perfused at 100 mm Hg via the aortic root. The Krebs/Pipes perfusate was bubbled with oxygen and kept at 37°C, its composition (in mM) was: NaCl 123, KCl 3.4, $MgSO_4 \cdot 7H_2O$ 1.2, Pipes 14.4, glucose 11.1, $CaCl_2 \cdot 2H_2O$ 2.5 titrated to pH 7.4 with NaOH. The composi-

tion of the 'ischaemic' perfusate was: NaCl 117, KCl 10.1, $MgSO_4 \cdot 7H_2O$ 1.2, Pipes 15.3, glucose 11.1, $CaCl_2 \cdot 2H_2O$ 2.5 and titrated to pH 6.4 with NaOH. The pH and potassium concentration of the 'ischaemic' buffer is similar to that found under conditions of ischaemia (Botting et al., 1985).

Left ventricular pressure was recorded from a saline-filled, non-compliant balloon kept at an end diastolic pressure of approximately 5 mm Hg. A pair of silver ball electrodes placed on the epicardial surface of the right atrium and the left ventricle were used to record an ECG. Hearts subjected to 'ischaemic' perfusate were perfused with normal buffer for 5 min prior to exposure to 'ischaemic' solution. Cumulative dose-response curve data were obtained for the actions of the drugs in normal and 'ischaemic' conditions.

2.4. Ischaemia-induced arrhythmias

Ischaemic arrhythmias were induced by occlusion of the left anterior descending coronary artery (Paletta et al., 1989) using the Lambeth conventions as guide lines (Walker et al., 1986). Briefly, anaesthetized rats were ventilated, their chest opened and a polypropylene suture loosely tied around the artery. The chest was closed and animals allowed to recover for 15 min. Drugs were infused continuously before and after occlusion starting 5 min prior to occlusion. Animals were monitored for 20 min after occlusion, a period which includes the first phase (5–10 min) of ischaemia-induced arrhythmias. At the end of this period hearts were excised and the size of the occluded zone estimated by perfusing the heart with a buffer containing cardiogreen. The occluded zone size was calculated as a percentage of total ventricular mass. All arrhythmias were recorded and summarized for each animal as an arrhythmia score (Curtis and Walker, 1988a). This arrhythmias score is a Gaussian distributed variable that takes into account the occurrence, severity and duration of arrhythmias. Blood pressure, heart rate and ECG variables were recorded in order to document drug effects prior to, and after, occlusion. The maximum R and 'S–T' segment elevation, as well as the time at which these maxima occurred, were recorded as in previous studies (Curtis and Walker, 1988b).

2.5. Acute toxicity studies in conscious rats

The right jugular vein of rats was cannulated under halothane anesthesia and the cannula subcutaneously tunneled to the back of the head. Wound sites were infiltrated with bupivicaine and animals allowed 3 h to recover from surgery. Infusions of the drug under test was maintained for 25 min while the animal was observed for signs of toxicity.

2.6. Data analyses

In order to summarize the actions of a drug on blood pressure, ECG, heart rate, and responses to electrical stimulation, cumulative dose-response curves were constructed. Bolus doses were given every 8 min in a dose-doubling cumulative manner and blood pressure, heart rate and ECG monitored continuously. Responses were measured at the peak of their responses. In infusion studies responses were measured when they had reached a plateau, approximately 1 min before the next dose. In electrical stimulation studies the infused dose was doubled every 5 min. All data points are expressed as mean ± S.E.M. for group of size 'n'. Repeated measures ANOVA was used to analyse cumulative dose-response data with Duncan's test for differences. Dose-response curves are drawn according to a logistic function (general form of $y = x^n/(a^n + x^n)$ where x is the dose, a is the effective dose for a 50% response and n is the slope factor-Hill coefficient). Maxima were defined as no arrhythmias

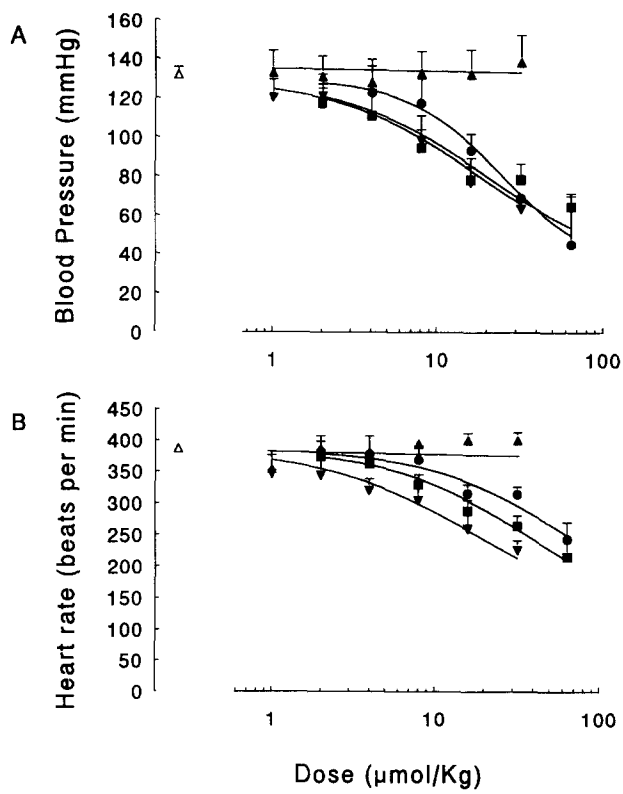

Fig. 1. Peak blood pressure and heart rate responses to bolus injections of drugs. Blood pressure (A) in mm Hg and heart rate (B) in beats/min were measured at the peak of the response to bolus injections of vehicle controls (▲), quinidine (■), lidocaine (●) or flecainide (▼) given cumulatively. Data points are the mean ± S.E.M. ($n = 5$). The open triangle symbols are the grouped pre-drug values ($n = 20$). All drug curves were statistically different from the controls.

for the antiarrhythmic study, a 90 mm Hg fall for blood pressure, a 250 beats/min fall in heart rate, and ECG intervals of 100 ms for PR, 50 ms for QRS and 150 ms for 'QT'. The maximum PR interval for isolated hearts was defined to be 200 ms. Our experience with rats suggests that these maxima are the largest values which are compatible with life. Potency is expressed in terms of the logarithm$_{10}$ of the dose in μmol/kg (bolus) or μmol/kg/min (infusions) required to produce a 25% change from pre-drug values (logD25%). ED_{50} values are not reported since determination of these values required excessive extrapolation.

3. Results

3.1. Haemodynamic and ECG response to class I antiarrhythmics

The potencies of the three drugs were calculated as logD25% values from dose-response curves such as

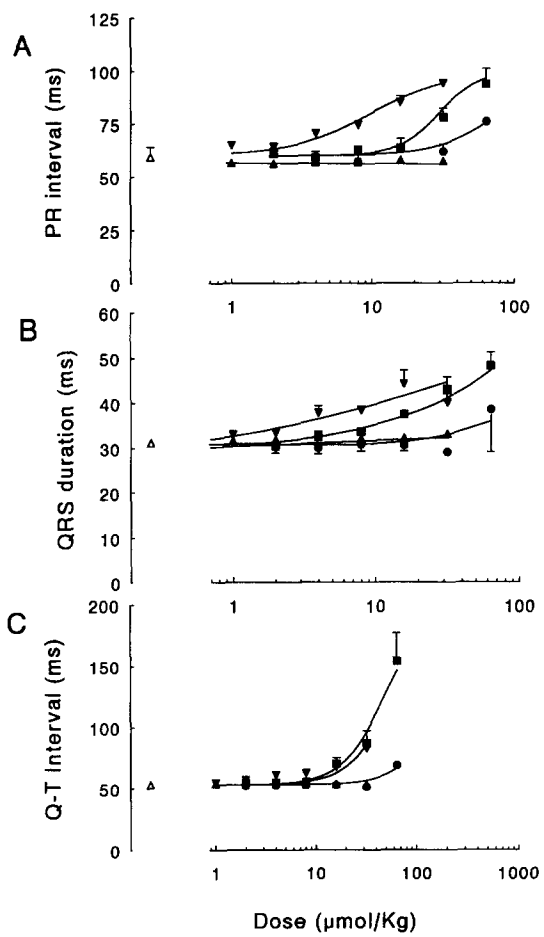

Fig. 2. Peak ECG responses to bolus injection of drugs. P–R intervals are shown in (A), QRS duration in (B) and 'QT interval' in (C), all in ms, for vehicle control (▲), quinidine (■), lidocaine (●) and flecainide (▼). Values are mean ± S.E.M. ($n = 5$). The open triangle symbols are the grouped pre-drug values ($n = 20$). These data were used to calculate the log D25% values.

Table 1
LogD25% estimates of the potencies of the three drugs for effects on electrical stimulation variables

Drug	iT	tT	VFT	ERP
Quinidine	0.7 ±0.3	0.7±0.2 *	0.09±0.07	0.3±0.05
Lidocaine	1.0 ±0.3	1.4±0.1 *	0.9 ±0.1 *	1.1±0.2 *
Flecainide	0.06±0.1 *	0.3±0.1 *	0.00±0.05	> 0.60

The logD25% value ± S.E.M. ($\log_{10}$ of dose, in μmol/kg/min, causing a 25% change from pre-drug values) for each drug was obtained by interpolation from individual dose-response curves in each of five rats. Drug effects included increase in thresholds for current (iT, μA), duration (tT, ms) and ventricular fibrillo-flutter (VFT, μA) or effective refractory period (ERP, ms). Pre-drug values for iT and VFT were 95 ± 10 μA and 170 ± 12 μA,respectively, and the corresponding pre-drug values for tT and ERP were 0.21 ± 0.08 ms and 40 ± 3 ms. All variables were increased by the drugs. * $P < 0.05$ for difference from other drugs.

those shown in Figs. 1 and 2 for bolus injections and for infusions (dose-response curves for infusions not shown). The three drugs were equi-potent in lowering blood pressure when given as boluses. When given by infusion quinidine was more potent (logD25% = 0.0 ± 0.2) than flecainide (logD25% = 0.6 ± 0.2) and lidocaine (logD25% = 0.7 ± 0.2). In terms of bradycardia the three drugs were equi-potent whether given by bolus (range of logD25% values 1.1 ± 0.3 to 1.3 ± 0.5) or infusion (range of logD25% values 0.5 ± 0.3 to 0.8 ± 0.1).

In terms of actions on the PR interval of the ECG flecainide was most potent (logD25% = 0.9 ± 0.1) and lidocaine (logD25% = 1.9 ± 0.3) least potent when the drugs were given as bolus injections. When given as infusions the same pattern of potency was seen (flecainide logD25% = 0.5 ± 0.2, quinidine logD25% = 1.0 ± 0.1 and lidocaine logD25% > 1.5). Exactly the same relative potencies were seen for QRS changes with flecainide being the most potent drug. The highest dose of lidocaine failed to produce a 25% increase in QRS (logD25% > 1.5). Lidocaine also failed to change the 'Q–T' interval whereas quinidine and flecainide were equi-potent in this regard. Thus lidocaine was not potent in terms of ECG effects but was approximately equi-potent with the other two drugs in terms of effects on blood pressure or heart rate.

3.2. Effects on electrical stimulation

Table 1 shows the potencies of the three drugs, given as infusions, in increasing resistance to electrical stimulation. All three drugs decreased myocardial excitability as assessed by increases in threshold current and duration for capture and threshold currents for induction of ventricular fibrillo-flutter. The potency rank order of the three drugs in terms of effects on the above variables paralleled those for widening PR and QRS intervals of the ECG. Flecainide was the most

potent followed by quinidine and finally lidocaine. Comparison of potencies for effects on ERP versus PR, QRS, iT, tT and VFT values revealed differences between the three drugs. Lidocaine was more potent for effects on ERP compared with effects on PR or QRS intervals. Flecainide was equi-potent in increasing PR, QRS and thresholds but lacked potency in terms of effects on ERP. Quinidine was intermediate between lidocaine and flecainide with respect to ERP versus PR, QRS and thresholds. Analysis of the effects of quinidine on ERP, with respect to the indices for Na^+ channel blockade, such as QRS and iT, was confounded by the fact that quinidine had marked effects on the 'Q–T' interval, presumably as a result of K^+ channel blockade.

3.3. Frequency dependence

In an attempt to assess the frequency dependence of action of the three drugs, threshold currents were assessed over a range of beating frequencies using infusion rates similar to those used in the coronary occlusion experiments. The results of this study (data not shown) were equivocal in that elevations in thresholds for all drugs were dependent upon frequency and dose, with lidocaine marginally showing the most dependency on frequency. The threshold currents for capturing the heart were elevated by all the drugs. For 2 and 4 μmol/kg/min quinidine, the elevation was 28 ± 4 (mean ± S.E.M.) and 40 ± 3 from pre-drug control values. For lidocaine, 8 and 16 μmol/kg/min, elevations were 33 ± 1 and 68 ± 2 while for 1.5 and 3 μmol/kg/min flecainide they were 35 ± 3 and 108 ± 5, respectively. Thus dose-related increases were greatest for flecainide and least for quinidine.

As a further possible measure of the frequency dependence of drug action a ratio was devised to compare a drug's potency in producing effects on the PR interval of the ECG versus potency for effects on thresholds for induction of ventricular fibrillo-flutter. Examples of the use of this ratio are shown in Fig. 3 where lidocaine was distinctly different from the other two drugs; it was 35–40 times more potent in terms of elevating ventricular fibrillo-flutter thresholds compared with increasing the PR interval of the ECG. With flecainide the ratio was not significantly different from unity. The PR interval was chosen since drugs were generally more potent in terms of prolonging this interval than in terms of widening the QRS. It is assumed that sodium currents play a considerable role in controlling atrioventricular conduction in rat hearts (Pugsley et al., 1993). Similar findings were obtained when the QRS and RSh were used.

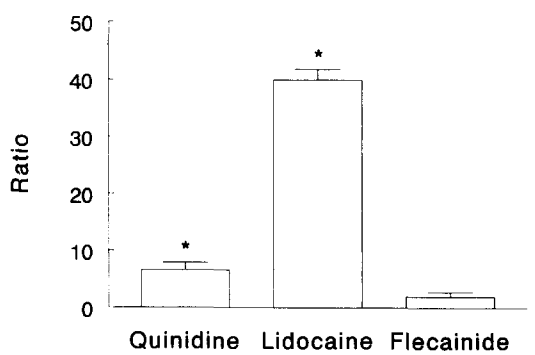

Fig. 3. Ratio of D25% estimates for PR prolongation to D25% for elevation of threshold currents for induction of ventricular fibrillo-flutter. The data used to calculate the ratios were interpolated from dose-response curves such as those seen in Fig. 2. * $P < 0.05$ for difference from unity.

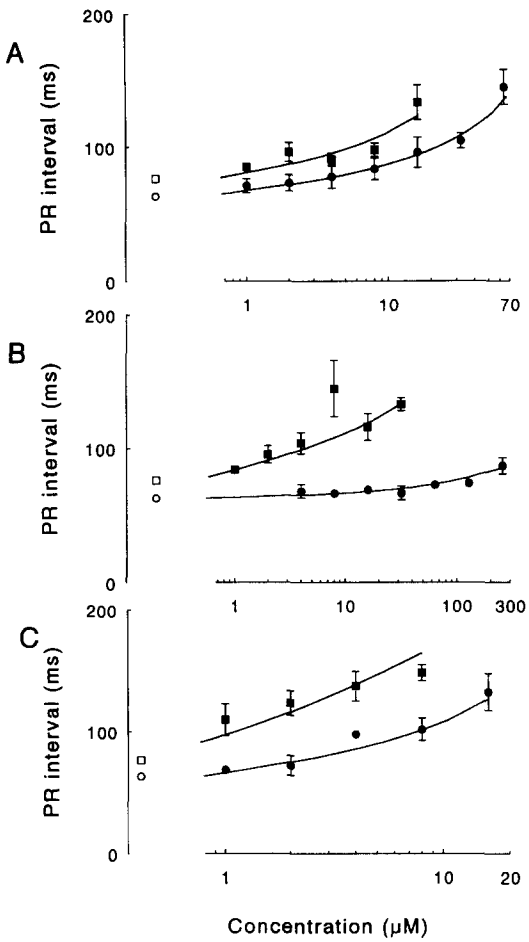

Fig. 4. Concentration-response curves for drug effects on P–R interval in isolated hearts perfused with normal (filled circles) or 'ischaemic' perfusate (filled squares). The drugs were quinidine (A), lidocaine (B) and flecainide (C). Points are mean ± S.E.M. for $n = 5$. The open symbols indicate the grouped mean pre-drug values ($n = 20$).

3.4. Effects on isolated hearts

In order to differentiate between effects mediated directly on the heart from those arising indirectly via

other components of the cardiovascular system, or because of pharmacokinetic factors, the potencies of the three drugs for changing ECG intervals were also determined in isolated hearts. Cumulative concentration-response curves, such as those shown in Fig. 4 for PR intervals, were obtained in isolated hearts in the presence of normal or 'ischaemic' perfusates. From such dose-response curves logD25% values were interpolated and such interpolated values are presented in Table 2. On a qualitative basis the results obtained in vitro paralleled those seen in vivo. All three drugs had similar potencies in hearts perfused at pH 7.4 and physiological concentrations of potassium. However, the potency of the three drugs was differently influenced by acidic pH and raised potassium concentrations. The potency of lidocaine was increased 105–340 times (depending upon the measure used) by the 'ischaemic' perfusate, whereas the potency of flecainide was minimally changed. The potency of quinidine was increased 2–4 times in the presence of the 'ischaemic' perfusate. During the course of this study it was noted that, at higher concentrations in normal perfusate, lidocaine induced asystole in 3/5 hearts whereas the other two drugs did not.

All three drugs decreased blood pressure and had bradycardic actions in vivo. The degree of bradycardia produced by the drugs was more marked in vitro. However, while all the three drugs lowered blood pressure in vivo, only quinidine reduced ventricular pressure in isolated hearts. Notably the three drugs were similar in their actions on blood pressure and heart rate as opposed to effects on the ECG, or electrical stimulation variables.

Table 2
LogD25% values for drug effects on ECG variables in isolated heart in the presence of normal or 'ischaemic' perfusates

Perfusate	Normal	'Ischaemic'	Ratio N/I
P–R			
Quinidine	0.9+0.2 *	0.6±0.2 *	2.0±1.1
Lidocaine	2.5±0.4 *	0.0±0.2	340 ±1.8 *
Flecainide	0.3±0.1 *	0.2±0.1	1.2±0.8
QRS			
Quinidine	1.4±0.1	0.8±0.04 *	3.9±1.1
Lidocaine	1.9±0.3	−0.1±0.2	105 ±1.6 *
Flecainide	0.7±0.05 *	0.3±0.2 *	2.6±1.3

Cumulative dose-response curves were obtained for quinidine, lidocaine and flecainide in isolated rat hearts in the presence of a normal or 'ischaemic' perfusate. PR and QRS indicate the usual ECG intervals. LogD25% concentrations (μM) were interpolated from the individual dose-response curves for five hearts and used to calculate an normal/ischaemic ratio for each heart. The group mean pre-drug values for the PR were 63±3 and 76±3 ms under normal and 'ischaemic' conditions, respectively. For the QRS duration the group mean pre-drug value under normal conditions was 32±3 ms whereas under ischaemic conditions it was 40±5 ms. * Statistical significance at $P < 0.05$ for a difference from other drugs.

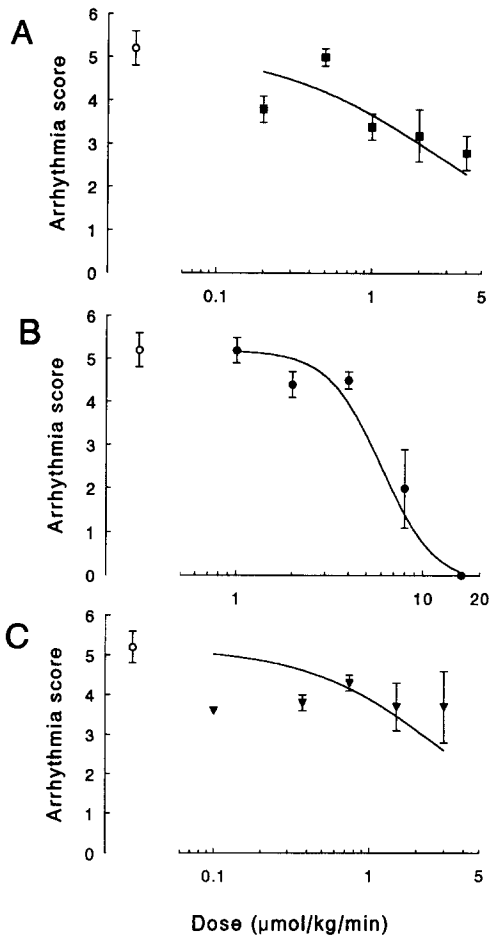

Fig. 5: Dose-response curves for antiarrhythmic effects of the drugs against ischaemia-induced arrhythmias. Various doses of quinidine (A), lidocaine (B) and flecainide (C) were tested for their ability to prevent the occurrence of ventricular arrhythmias in anaesthetized rats subject to coronary occlusion. Each point is the group mean arrhythmia score ± S.E.M. ($n = 7–9$). The mean arrhythmia score for the accumulated control group is shown in open symbols ($n = 18$). Inequality of variance in some groups was due to some of the animals in the group having very high arrhythmia scores and others low scores.

3.5. Effects on ischaemia-induced arrhythmias

Fig. 5 and Table 3 summarize the effects of the drugs on ischaemia-induced arrhythmias in intact rats. Table 4 is a summary of the combined effects of drug treatment (high and low dose infusions) and occlusion. Prior to occlusion the effects of the drugs on blood pressure and heart rate were similar to those obtained in the infusion study. It can be seen in Table 4 that these effects became more marked after occlusion. The higher infusion levels of all of the drugs produced marked vasodepression and bradycardia. The antiarrhythmic effectiveness varied markedly with the drug considered such that lidocaine, at the highest dose, gave complete protection while the other two drugs, particularly flecainide, were less effective in preventing arrhythmias.

Table 3
Antiarrhythmic activity of representative regimens against ischaemia-induced arrhythmias

Drugs	Log VPB	VT	Log VT dur	VF	Irr VF
Vehicle control	2.0±0.4	18/18	1.3±0.1	13/18	8/18
Quinidine 2	1.7±0.1	8/9	1.5±0.2	0/9 *	0/9 *
Quinidine 4	1.4±0.2	8/9	0.7±0.3	0/9 *	0/9 *
Lidocaine 8	1.0±0.3	2/9 *	2.0±0.1	2/9 *	0/9 *
Lidocaine 16	NE	0/9 *	NE	0/9 *	0/9 *
Flecainide 1.5	1.5±0.5	8/9	1.5±0.3	2/9 *	1/9
Flecainide 3	1.8±0.3	5/9 *	1.2±0.4	1/9 *	0/9 *

Rats were subjected to infusions (μmol/kg/min) beginning 5 min before occlusion and continuing thereafter. All arrhythmias were recorded in the 20 min period after occlusion as premature ventricular beats (VPB), ventricular tachycardia (VT) and ventricular fibrillation (VF). Log VPB is the mean of $\log_{10}$ of the number of VPBs occurring in each animal. The duration of VT (VT dur) was similarly $\log_{10}$ transformed to give a Gaussian distributed variable. VT indicates the number of animals in the group having ventricular tachycardia and VF those with ventricular fibrillation. * Statistical significance at $P < 0.05$ for difference from control. NE indicates no estimate made since no VPB nor VT were recorded.

Fig. 5B shows a clear dose-response relationship for the antiarrhythmic actions of lidocaine against ischaemia-induced arrhythmias. This was not the case for the other two drugs (Fig. 5A and C). There appeared to be a loose dose-response relationship for quinidine whereas flecainide had limited antiarrhythmic effectiveness which was not clearly dose-related. Flecainide at the higher doses increased the variance of the antiarrhythmic response such that at these doses some of the animals showed a reduction in arrhythmias whereas in others the arrhythmias may have been worsened.

All control animals subjected to coronary artery occlusion showed 'S–T' segment elevation. However, in drug-treated groups not all animals showed 'S–T' segment elevation. In those treated animals which showed 'S–T' segment elevation there was a trend towards delaying the time required to reach maximum elevation of the segment. The highest dose of lidocaine prevented 'S–T' segment elevation while the 8 μmol/kg/min dose appeared to delay and reduce the maximum 'S–T' segment elevation. None of the other drug-treated groups had a significant effect on maximum 'S–T' segment elevation. Similarly, none of the drugs showed consistent effects on the time required to reach an R wave maximum nor on the size of the R wave maximum (data not shown).

Table 4
Drug effects after occlusion

Drug	BP	HR	PR
Vehicle	1± 9	6±10	7.6±2.8
Quinidine 2	−39± 7 *	−138±19 *	28 ±9 *
Quinidine 4	−42± 8 *	−113±31 *	27 ±6 *
Lidocaine 8	−51± 6 *	−135± 8 *	25 ±6 *
Lidocaine 16	−55± 6 *	−165±15 *+	28 ±5 *
Flecainide 1.5	−49±11 *	−169±31 *	40 ±10 *
Flecainide 3	−53±25 *	−310±51 *+	87 ±9 *+

Infusions (μmol/kg/min) of quinidine, lidocaine and flecainide were begun 5 min before occlusion and continued for 20 min. Drug effects are mean changes±S.E.M. from pre-drug values. Initially $n = 9$ except in controls where $n = 18$ but after occlusion $n < 9$ due to the death of animals. Mean pre-drug blood pressure (BP) varied from 120±9 to 97±6 mm Hg and heart rate (HR) from 347±25 to 387±15 beats/min. The pre-drug PR interval (ms) varied from 61±2 to 66±1. * Statistical significance at $P < 0.05$ for a difference from vehicle, + $P < 0.05$ from the lower dose of the same drug.

3.6. Acute toxic effects in conscious rats

In a separate experiment with the three drugs the acute toxic effects of two infusion regimens which provided antiarrhythmic protection were examined in conscious rats. When given at a concentration of 8 μmol/kg/min lidocaine produced convulsions in 1 out of 3 animals tested whereas the 16 μmol/kg/min infusion produced convulsions in 3 out of 3 animals tested. On the other hand neither 2 or 4 μmol/kg/min quinidine produced convulsions although both infusions produced ataxia and sedation with the higher infusions producing collapse of animals. Flecainide produced less toxicity; ataxia and sedation were only observed with the high infusion level (3 μmol/kg/min).

4. Discussion

The mechanisms by which ischaemia produces arrhythmias are not known with certainty but it is believed that re-entry is an important mechanism (Cranfield et al., 1973). Such re-entry circuits involve both normal and ischaemic tissue. Ischaemia-induced arrhythmias could therefore be prevented by breaking the re-entry circuit, either in normal or ischaemic tissue. Thus a class I antiarrhythmic drug could prevent such arrhythmias by either acting on normal, or ischaemic tissue. However, many class I antiarrhythmics act to slow conduction in normal tissue and this can actually contribute to the generation of re-entry circuits (Dhein et al., 1993; Hondeghem, 1987; Roden, 1994). On the other hand, class I antiarrhythmics could prevent ischaemia-induced arrhythmias by abolishing conduction in already depressed ischaemic tissue (Janse, 1992). In this regard tetrodotoxin, a specific Na^+ channel blocker, has been shown to prevent ischaemia-induced arrhythmias in vitro and in vivo and circumstantial evidence suggests that tetrodotoxin may have some selectivity of action on ischaemic tissue (Abraham et al., 1989; Duff et al., 1988). Thus, in order to be effective in the setting of acute myocardial ischaemia, Na^+ channel blocking drugs must be potentated by ischaemic conditions and the high frequencies

of tachyarrhythmias. Furthermore, such a drug would have to be selective for cardiac tissue in order to avoid adverse effects due to actions on neuronal or vascular tissue.

It is unlikely that re-entry is the only mechanism of arrhythmogenesis in the setting of acute myocardial ischaemia and triggered activity secondary to cytosolic calcium overload may play a role (Pogwizd and Corr, 1987). Regardless of the mechanism of arrhythmogenesis it is clear that ischaemia-selective and frequency-dependent drugs will be more effective at abolishing ischaemia-induced arrhythmias. Thus the selectivity for Na^+ channel blocking drugs defined herein is appropriate regardless of the mechanism of arrhythmogenesis in the setting of acute myocardial ischaemia.

Of the three drugs tested, only lidocaine offered complete protection against the arrhythmias induced by coronary artery occlusion. Notably lidocaine was the only drug which showed marked 'ischaemia' dependency when tested on isolated hearts and, in addition, appeared to have marked frequency-dependent actions. Flecainide showed the least ischaemia dependency, and was also the least effective antiarrhythmic, whereas quinidine was marginally better both in antiarrhythmic actions and in the other two attributes.

Well established experimental evidence supports the idea that lidocaine shows selectivity for ischaemic conditions and for high frequencies. For example Davis et al. (1985) have shown in anaesthetized mongrel dogs, with ligation of the left anterior descending coronary artery, that the concentration of the drug in ischaemic myocardium correlated best with the antiarrhythmic response whereas the concentration in normal myocardium, or blood, did not. A number of studies have shown electrophysiologically that lidocaine abolishes re-entry in the ischaemic zone (El-Sherif et al., 1977; Kupersmith, 1979). In guinea-pig ventricular myocardium superfused with a simulated ischaemic solution (pH 6.4 and $[K^+] = 11.2$ mM) lidocaine exerted greater selectivity for ischaemic tissue than encainide (Campbell and Hemsworth, 1990). Further in vitro evidence has demonstrated that lidocaine acts preferentially at high frequencies (Sanchez-Chapula et al., 1983).

Despite lidocaine providing almost complete protection against ischaemia- induced arrhythmias in anaesthetized animals, the highly protective dose could not be used in conscious animals since it caused convulsions. This finding with lidocaine parallels those made previously with mexiletine (Igwemezie et al., 1992). Thus mexiletine gave 100% protection against ischaemic arrhythmias, but only at doses which caused convulsions. The actions of lidocaine and mexiletine in producing convulsions are not unexpected in view of the lipid solubility of both drugs. Indeed, mexiletine preferentially accumulates in the brain rather than in the target organ which is the heart (Igwemezie et al., 1992). In addition it should be remembered that action potential frequency is higher in neurons than in the heart. Thus a frequency-dependent drug would be most active on neuronal tissue.

It appeared that while lidocaine has selectivity for tachyarrhythmias, and for the conditions of ischaemia, it was insufficiently cardiac selective to confer usable protection against ischaemia-induced arrhythmias in conscious rats. Apparently neither of the other two drugs tested had sufficient selectivity for conditions of ischaemia, nor sufficient frequency dependence, to confer clear and unequivocal antiarrhythmic protection against ischaemia-induced arrhythmias. However, unlike lidocaine, neither quinidine nor flecainide appeared to produce signs of severe neuro-toxicity and thus may be more cardio-selective than lidocaine.

All of the drugs tested possess antifibrillatory actions while antiarrhythmic actions against other arrhythmias varied remarkable (see Table 3 and Fig. 5). The ischaemia selectivity and frequency dependence shown by lidocaine probably account for its antifibrillatory and antiarrhythmic actions. Quinidine and flecainide demonstrated limited antiarrhythmic actions but did reduce the incidence of ventricular fibrillation significantly. It is not clear what the mechanism for this effect is but it might be related to blockade of K^+ channels. Both flecainide and quinidine are known to block K^+ channels in the heart (Colatsky et al., 1990). Indeed, our data shows that quinidine prolongs the 'QT' interval significantly at a dose (16 μmol/kg i.v. bolus) that did not significantly increase any of the indices of Na^+ channel blockade. K^+ channel blockade in the rat heart has been reported to be selectively antifibrillatory (Adaikan et al., 1992).

The antiarrhythmic dose of lidocaine prevented 'S–T' segment elevation of the ECG caused by myocardial ischaemia which might be attributed to an anti-ischaemic effect; however, this possibility seems unlikely for a number of reasons. The occluded zone size (zone at risk) was not significantly different in any of the groups (data not shown). As collateral blood flow in this species is very small, even profound vasodilatation can be expected to have little effect on blood flow to the ischaemic myocardium (Maxwell et al., 1984). Furthermore, similar vasodilatation (as assessed by drug effects on blood pressure) was seen with all three drugs rendering any putative anti-ischaemic effects equal for all groups, while only the highest dose of lidocaine suppressed 'S–T' segment elevation. Similar findings were obtained by Abraham et al. (1989) with antiarrhythmic doses of tetrodotoxin. The mechanism by which lidocaine prevented 'S–T' segment elevation is likely to be due to suppression of the inward sodium current in the ischaemic cells to such an extent that they were rendered inexcitable and electrically silent.

Silencing cells in the ischaemic zone, which show delayed activation and shortening of the action potential duration, would leave the remainder of the myocardial depolarization and repolarization cycle in phase and thus no 'S–T' segment elevation would be observed. No consistent effects on 'S–T' segment elevation were noted in any group other than the highest dose of lidocaine, similarly none of the other treatments produced complete antiarrhythmic protection. It is tempting to suggest that an effective dose of an ischaemia-selective Na^+ channel blocking drug will suppress 'S–T' segment elevation without effecting the size of the ischaemic zone.

In addition to lacking sufficient selectivity for the pathology underlying ischaemic arrhythmias, or for cardiac versus neuronal tissue, all three drugs showed a lack of cardiac versus vascular selectivity. Thus all three drugs produced marked lowering of blood pressure. It is sometimes assumed that class I drugs are direct cardiac depressants and that this is partly the reason for the hypotensive actions of such drugs (Hammermeister et al., 1972). However, in our study the falls in blood pressure seen with class I antiarrhythmics were not always associated with corresponding depression of left ventricular pressure in isolated hearts. In a comparative study of a series of class I antiarrhythmics the order of potency for negative inotropic effects of drugs did not correlate directly with Na^+ channel blocking actions (Matsumoto et al., 1993). Honerjager et al. (1986) showed in a comparison of seven class I antiarrhythmics that some of the drugs were more potent Na^+ channel blockers than negative inotropic agents, while the reverse was true for others. The molar ratios for the two actions ranged from 0.23 for sparteine to 2.2 for disopyramide. With two exceptions, all of the drugs produced a larger negative inotropic effect than tetrodotoxin at concentrations equi-effective in Na^+ channel blockade. Thus the fall in blood pressure produced by the three drugs in this study could have been due to vasodilatation, rather than to the limited direct cardiac depression seen in vitro.

Thus by a variety of measures none of the representative antiarrhythmics tested in this study showed sufficient selectivity for ischaemic myocardium which would offer complete protection against the arrhythmias induced by myocardial ischaemia in conscious animals.

Acknowledgements

The help of Sandro Yong with certain experiments is acknowledged as is partial support from the Heart & Stroke Foundation of British Columbia and the Yukon and Rhythm Search Developments Ltd.

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