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The antifibrillatory potency of aprindine, mexiletine, tocainide and lignocaine compared on Langendorff-perfused hearts of rabbits and guinea-pigs

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The effectiveness of three new antiarrhythmic drugs, aprindine, mexiletine and tocainide in elevating ventricular fibrillation threshold measured in the Langendorff-perfused rabbit heart and in protecting against ouabain-induced arrhythmias in the Langendorff-perfused guinea-pig heart has been compared with that of lignocaine. All these drugs have produced a significant rise in the threshold but quantitatively mexiletine was about equal to, tocainide five times less and aprindine thirty-eight times more potent than lignocaine in this effect. Aprindine differed from the other three drugs in that it had a slow onset of action and its effect was not entirely removed upon reperfusion with the drug-free solution. Only aprindine and mexiletine provided complete protection against ouabain-induced ventricular fibrillation while 3 of 6 and 4 of 6 hearts fibrillated in the presence of lignocaine or tocainide respectively.

There is a great need for an effective antiarrhythmic drug in the management of ventricular arrhythmias after acute myocardial infarction and in prophylaxis of ventricular fibrillation. In recent years, several new compounds have been introduced (Zipes & Troup 1978). Aprindine, mexiletine and tocainide are examples of these drugs, which have prominent local anaesthetic properties and, in fact, mexiletine and tocainide are closely related to lignocaine in chemical structure. The effectiveness of these compounds in experimental arrhythmias (Georges et al 1973; Allen et al 1972; Coltart et al 1974), clinical evaluation (Fasola & Carmichael 1974; Talbot et al 1973; McDevitt et al 1976), and electro-physiological studies (Verdonck et al 1974; Singh & Vaughan Williams 1972; Moore et al 1978) have all established them as effective antiarrhythmic agents and indicated a resemblance to lignocaine in the mode of action. These drugs have been compared separately with conventional antiarrhythmic agents using different methods (Foster et al 1976; Steinberg & Greenspan 1976; Jewitt et al 1977; Schnittger et al 1978). The purpose of this study was to investigate the antifibrillatory properties of these three new drugs and to compare their potency with that of lignocaine under the same experimental conditions using two models, an electrically-induced and a drug-induced ventricular fibrillation in the Langendorff-perfused heart of rabbits and guinea-pigs.

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METHODS

Electrically-induced fibrillation in the Langendorff-perfused rabbit heart

New Zealand White rabbits of either sex, 0·9–1·5 kg, were killed by a blow on the head and bled. The heart was rapidly removed and placed in McEwen's solution (1956) containing in mmol litre^{-1}: NaCl 130, KCl 5·6, $CaCl_2$ 2·2, NaH_2PO_4 0·9, $NaHCO_3$ 25, glucose 11 and sucrose 13. This was gassed with 95% O_2 and 5% CO_2 and the pH was 7·3 to 7·4. The aorta was immediately cannulated and coronary perfusion was started at a pressure of about 6 KPa (60 cm H_2O) at 37 °C. Perfusion with pure McEwen's solution or this solution with a drug could be selected by turning a tap. A small stainless steel hook was passed through the ventricular apex and connected to a force displacement transducer, by which the amplitude of contraction was recorded on one channel of an oscillograph. Two silver-silver chloride wires were connected to the heart through two wick electrodes which were placed on the anterior surface of the base of the two ventricles to record the electromyogram. This was displayed on an oscilloscope (Airmec type 279) and was recorded on a second channel of the oscillograph. The heart was stimulated through the hook attached to the apex and another connected to the base of the left ventricle. In order to test whether there was likely to be mechanical

trauma affecting the threshold of the tissue in which the former hook was fixed, some experiments were done in which a third hook, near the apex and not attached to any transducer, was used as a stimulating electrode alternately with the apical hook. The results showed that the thresholds did not vary according to which of these two hooks was used as an electrode and so it was decided to use the one attached to the apex throughout the study and save piercing the heart by an extra hook. The stimulating electrodes were linked to an isolated battery-powered constant current stimulator. The current multiplier control was turned by a dc motor and gearbox to increase the current intensity at a constant rate. A period of at least 40 min of spontaneous beating was always allowed for coronary flow, heart rate, amplitude of contraction and the electromyogram to stabilize before stimulation commenced. To determine the ventricular fibrillation threshold (VFT), serial rectangular impulses of 3 ms duration at a frequency of 20 Hz were used. The current was increased at a rate of 30 μA s^{-1}. The minimum current required to induce ventricular fibrillation was taken as the VFT. The moment fibrillation was induced, stimulation was stopped and if normal rhythm had not returned in 60 s, defibrillation was effected by infusing 0·1 ml of 0·54 mol $litre^{-1}$ potassium chloride into the aortic cannula. In each experiment three determinations of the threshold were carried out at 15 min intervals and the mean was taken as the control value. The heart was then perfused with McEwen's solution containing the test drug and the threshhold was determined after 15, 30 and 60 min exposure to the drug. The heart was then reperfused with the drug-free solution and three determinations were carried out after 15, 30 and 60 min.

Ouabain-induced arrhythmias in the Langendorff-perfused guinea-pig heart

Guinea-pigs of either sex, 400–500 g, were used. The method for perfusion and recording was as described above for rabbit hearts. The electromyogram was recorded on tape for further analysis. Ouabain was infused into the aortic cannula at a rate of 5·48 μmol per min. The test drug was added to the perfusion solution 5 min before ouabain infusion was started and perfusion with both continued throughout the experiment. The time of ouabain infusion required to produce unequal R-R interval, ventricular fibrillation and cardiac arrest in the presence of the test drug was compared with that in ouabain control experiments.

RESULTS

VFT determination in the Langendorff-perfused rabbit heart

VFT was determined in 78 rabbit hearts. In 67 VFT values ranged between 0·1–3·4 mA and for the other 11 between 6·5–13·7 mA. On six hearts, VFT was determined in the absence of any drug throughout the experiments. In all these the threshold, within 1 h of its first determination, dropped by 14–19·5% of its original value and then remained within these limits over 2 h. Perfusion with various concentrations of all tested drugs produced a significant rise in VFT but no significant changes were observed in coronary flow, heart rate, amplitude of contraction or the electromyogram. In Fig. 1 the percentage change in VFT from control values, determined for each heart

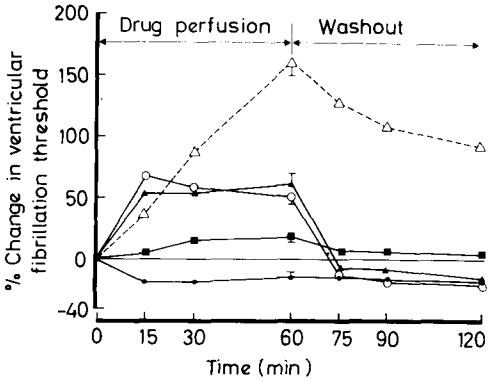

FIG. 1. Percentage changes in VFT in relation to time of exposure (and washout) to lignocaine (▲) 3·46 μmol $litre^{-1}$, aprindine (△) 0·28 μmol $litre^{-1}$, mexiletine (○) 4·64 μmol $litre^{-1}$ and tocainide (■) 4·36 μmol $litre^{-1}$. The change in VFT for the untreated hearts (●) is also plotted. Note: concentration of aprindine is about twelve times less than the other drugs.

before starting perfusion with the drug, is plotted against perfusion (and washout) time with lignocaine (3·46 μmol $litre^{-1}$), aprindine (0·28 μmol $litre^{-1}$), mexiletine (4·64 μmol $litre^{-1}$) and tocainide (4·36 μmol $litre^{-1}$). The change in VFT for the untreated group is also plotted for comparison. Mexiletine increased VFT to about the same level as did lignocaine and this effect of both drugs was completely removed on washout. Perfusion with a comparable concentration of tocainide produced a rise in VFT which was less than one third of that produced by lignocaine. In contrast, aprindine in a concentration twelve times less than that of lignocaine caused a rise in the threshold which was about three times that produced by lignocaine. This effect was only decreased but not entirely removed during one hour of

reperfusion with the drug-free solution. Additional concentrations of each drug were tested in order to plot dose-response curves of their effect on VFT after 60 min exposure to each drug. The results are plotted in Fig. 2, which shows a considerable difference between them in potency but the curves are approximately parallel. From Fig. 2 the concentration

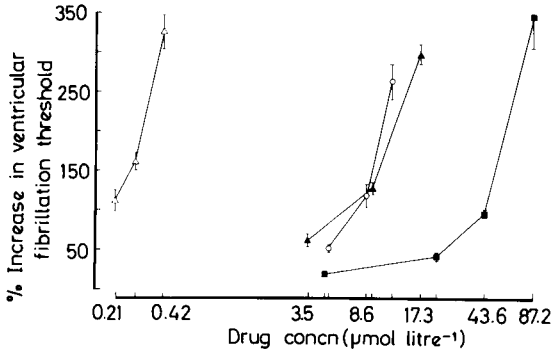

FIG. 2. Dose-response curves of the effect of lignocaine (▲), aprindine (△), mexiletine (○) and tocainide (■) on VFT, after 60 min exposure to each drug. Abscissa: drug concentration on a log scale. Ordinate: percentage increase in VFT. Each point is the mean ± s.e. of six experiments.

required to raise VFT to 200% above its original value was determined for each drug and accordingly their potency has been compared with that of lignocaine used as a standard with a potency of 1 (Table 1). Since the rise in VFT induced by aprindine continued steeply as the duration of exposure to the drug increased, additional experiments were carried out in which the drug was left in contact with the preparation for 2 h. The results showed that aprindine did not increase VFT more than the level achieved after 1 hour exposure to the drug.

Ouabain-induced arrhythmias in the Langendorff-perfused guinea-pig heart

Infusion of ouabain into the aortic cannula of a Langendorff-perfused guinea-pig heart produced the sequence of cardiac arrhythmias reported by Vaughan Williams & Sekiya (1963) on anaesthetized guinea-pigs. In all experiments, unequal intervals between beats appeared before extrasystoles developed. Ventricular fibrillation occurred in 16 of 16 hearts receiving ouabain alone. Lignocaine in two concentrations (1·73 and 3·46 μmol litre^{-1}), aprindine (0·28 μmol litre^{-1}), mexiletine (4·64 μmol litre^{-1}), and tocainide (4·36 and 21·8 μmol litre^{-1}) were tested by this method. The results are summarized in Table 2.

Table 1. Effectiveness of aprindine, mexiletine and tocainide compared with that of lignocaine in raising VFT. Isolated rabbit heart.

	TD200* (μmol litre^{-1})	Relative potency
Lignocaine	11·6	1·0
Aprindine	0·31	38·1
Mexiletine	9·9	1·2
Tocainide	58·3	0·2

* TD200, the concentration required to raise VFT to 200% above its original value.

Table 2. Effect of aprindine, mexiletine and tocainide compared with that of lignocaine on ouabain-induced cardiac arrhythmias. Isolated guinea-pig heart.

		Mean (± s.e.) time of ouabain infusion (min) required to produce		
(μmol litre^{-1})	n	Unequal R-R interval	Ventricular fibrillation*	Ca diac arrest
Control	16	3·6 ± 0·26	20·3 ± 1·6 (16/16)	72·3 ± 5
Lignocaine 1·73	6	4·3 ● 0·75	30 ± 2·9^{b} (4/6)	91 ± 8^{a}
3·46	6	5·5 ± 0·35^{c}	48 ± 13^{c} (3/6)	122 ± 9^{c}
Aprindine 0·28	6	7·2 ± 1·2^{c}	(0/6)	184 ± 7^{c}
Mexiletine 4·64	6	4·7 ± 0·8^{a}	(0/6)	147 ± 9^{c}
Tocainide 4·36	6	3·8 ± 0·47	29 ± 5^{a} (4/6)	89 ± 8·5
21·8	6	4·7 ± 0·3^{a}	82 ± 24^{c} (2/6)	157 ± 15^{c}

* The incidence of ventricular fibrillation is given in brackets. Statistical significance (*t*-test) of the difference from control: a: $P < 0·05$, b: $P < 0·01$, c: $P < 0·0005$.

Only aprindine and mexiletine provided complete protection against ouabain-induced ventricular fibrillation while 3 of 6 and 4 of 6 hearts fibrillated in the presence of lignocaine or tocainide, respectively. However, the time of ouabain infusion required to induce fibrillation in these hearts was significantly higher than in control for both lignocaine ($P < 0·0005$) and tocainide ($P < 0·05$). With all the antiarrhythmic drugs there was also a significant increase in the time of ouabain infusion required to cause cardiac arrest.

DISCUSSION

The antifibrillatory potencies of aprindine, mexiletine and tocainide were compared with that of lignocaine. Qualitatively, all these drugs proved to be effective in elevating VFT and in protecting against ouabain toxicity. Our finding that aprindine was clearly the most potent drug is consistent with the observations of Foster et al (1976) who, experimenting on dogs, compared aprindine with other antiarrhythmic drugs in suppression of particular ouabain-induced rhythms which they defined as accelerated ventricular escape and repetitive ventricular response. They found that different drugs, including quinidine,

procainamide, phenytoin, propranolol and lignocaine, were successful only in 0–33% of trials, while aprindine suppressed these rhythms in 14 of 14 dogs. In a study on canine cardiac tissue (Steinberg & Greenspan 1976) aprindine was found to be much more potent than lignocaine in affecting the electrophysiological properties underlying their antiarrhythmic effect. The difference we found between aprindine and the other three drugs in the time course of their effect in elevating VFT and the decrease in VFT during the washout period is well in accord with two electrophysiological studies. In the first, Verdonck et al (1974) found a slow onset of action and long-lasting effects of aprindine on transmembrane potentials. They supported this by their finding that the uptake and release of radio-active aprindine from isolated heart preparations was slow. Similarly, Steinberg & Greenspan (1976) found aprindine to have a prolonged onset of action in comparison with lignocaine and a slow rate of recovery during perfusion with the drug-free solution ($\geqslant 2$ h) while that of lignocaine was rapid (~ 15 min).

On the other hand, mexiletine, which has been characterized by Singh & Vaughan Williams (1972) as having typical 'class 1' antiarrhythmic action like that of quinidine, procainamide and lignocaine (Vaughan Williams 1970) and as being equal to lignocaine in local anaesthetic potency, was found in the present study to be about equipotent to lignocaine in raising VFT. Complete protection against ouabain-induced ventricular fibrillation was achieved in all hearts perfused with mexiletine while 3 of 6 hearts fibrillated in the presence of lignocaine (Table 2). Similarly, mexiletine has been found to be equal to phenytoin in preventing ventricular arrhythmias induced by the intravenous infusion of adrenaline in dogs breathing halothane mixtures and in abolishing ventricular ectopic beats which occurred in conscious dogs after coronary artery ligation, but it was more effective than phenytoin against ouabain-induced ventricular tachycardia (Allen et al 1972). The results of our experiments with tocainide are in agreement with those of Schnittger et al (1978) in the sense that tocainide was less effective than lignocaine in raising VFT, but effects of both drugs are detectable at concentrations less than they have reported. This discrepancy could be accounted for by the well-known differences between whole animal and isolated organ experiments as well as species differences. In anaesthetized dogs, they found no effect on VFT at tocainide plasma concentrations less than 6–10 μg ml^{-1} (26–43·6 μmol litre^{-1}) and an average of 71% increase at a concentration of 20 μg ml^{-1} (87 μmol) litre^{-1}. However, they have also reported no measurable effect on VFT of lignocaine at plasma concentrations below 1·3–4 μg ml^{-1} (4·5–13·8 μmol) litre^{-1}. The efficacy of tocainide has recently been assessed in man (McDevitt et al 1976; Ryan et al 1979). These studies show that tocainide given orally has effectively suppressed ventricular ectopic beats.

Although it is well recognized that in the clinical situation important factors, such as absorption, half-life and side effects of a new drug determine its value in therapy, quantitative information on the effectiveness of this drug compared with others in different experimental conditions could still be considered essential for its assessment. The results of this study provide a comparison of the antifibrillatory potency of three new antiarrhythmic drugs of which aprindine appears to be a powerful agent. However, aprindine has a narrow margin of safety as shown by a clinical study (Van Durme et al 1974) its mean effective plasma concentration was 1·35 μg ml^{-1} (3·7 μmol litre^{-1}) and neurological side effects appeared at plasma concentration of 2·65 μg ml^{-1} (7·4 μmol litre^{-1}).

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