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A comparison of the effects of bethanidine, meobentine and quinidine on the electrical activity of rat hearts *in vivo* and *in vitro*

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1 Glass microelectrodes were used to record transmembrane electrical activity from cells located just beneath the endocardial surface of segments of the right ventricular free wall of the rat heart during superfusion and electrical stimulation *in vitro* at 37°C.

2 The sulphates of bethanidine, meobentine or quinidine (4 to 20 μM) applied *in vitro* caused a prolongation of action potential duration and a delayed and slowed return of electrical excitability following an action potential.

3 Intracardiac electrical stimulation of the urethane-anaesthetized rat heart *in situ* was used to measure ventricular refractory periods from the electrocardiogram.

4 Intravenous administration of bethanidine, meobentine or quinidine (10 to 20 mg kg^{-1}) caused a prolongation of ventricular refractory periods. Quinidine had a briefer duration of action than either of the other two drugs tested.

5 Urethane-anaesthetized open-chested rats which were subjected to left coronary artery occlusion displayed ventricular tachyarrhythmias in their electrocardiogram. These arrhythmias occurred during the period of occlusion and even more prominently after release of the occlusion. Intravenous administration of bethanidine, meobentine or quinidine (1 to 20 mg kg^{-1}) protected rats against these arrhythmias. The protective effect of quinidine was briefer than that of either of the other two drugs tested.

Introduction

Bethanidine was developed originally as an orally-active adrenergic neurone blocking agent for the treatment of arterial hypertension (Boura & Green, 1963). Later the drug was also found to possess a useful anti-arrhythmic activity (Leveque, 1966; Bacaner & Benditt, 1982; Bacaner *et al.*, 1982; Benditt *et al.*, 1984; Patterson *et al.*, 1984). However, doubts and disagreements have been expressed concerning the pharmacological mechanisms whereby these anti-arrhythmic effects are produced (Bacaner *et al.*, 1982; Patterson *et al.*, 1984). Unfortunately, the therapeutic usefulness of bethanidine as an anti-arrhythmic agent is limited not only by these uncertainties but also by the production of marked orthostatic hypotension, the latter consequent upon interruption of sympathetic nerve activity. Meobentine, a methoxylated derivative of bethanidine, lacks adrenergic neurone blocking activity but retains the anti-arrhythmic activity of the parent molecule (Touw *et al.*, 1977; Wang *et al.*, 1977; Michelson *et al.*, 1981; Wastila *et al.*, 1981). However, direct comparison of bethanidine and meobentine as anti-arrhythmic agents does not seem to have been undertaken previously either *in vivo* or *in vitro*. In order to facilitate comparisons, all experiments in the present study were performed on the heart of a single species, namely the rat.

Methods

Male albino rats of the Sprague-Dawley strain weighing 340 to 410 g were used for these experiments.

In vitro *experiments*

Strips of muscle measuring approximately 3 by 8 mm were prepared from the right ventricular cardiac free wall of freshly killed animals and placed, unless otherwise specified, in a solution, at 37°C, of the

following composition (mM): NaCl 138, KCl 5, $CaCl_2$ 2, $MgCl_2$ 2, NaH_2PO_4 0.5, $NaHCO_3$ 10 and glucose 10, and gassed with a mixture of 95% O_2 plus 5% CO_2, giving a pH of 7.2. Transmembrane potentials (V_m) from muscle cells situated just beneath the endocardial surface were recorded with glass microelectrodes and transmitted via a single-ended high input-impedence coupler unit (Type 8124, made by C.F. Palmer) to an oscilloscope for continuous visual display. The coupler had facilities for capacitance neutralization and was readjusted before each set of recordings. Recorded voltage signals were also digitized and stored in a transient store microprocessor (Type 140, made by Bioscience). Stored signals could be replayed from this device at speeds of up to 2000 fold slower than those at which they were recorded, permitting action potentials to be printed without distortion on paper, using a conventional pen recorder. The transient store microprocessor also permitted the maximum rate of change of V_m ($\dot{V}_{max}$) during phase 0 of the action potential to be measured. Values of $\dot{V}_{max}$ provide a convenient measure of the availability of the fast sodium channel for current flow, as shown previously by Gettes & Reuter (1974). The muscle was stimulated via a pair of platinum wires with square wave pulses, each of 10 V and 1 ms duration at a rate of 1 Hz unless otherwise specified in the text. Facilities were available not only to stimulate the muscle with single pulses, but also, once every 20 s, to provide a pair of stimuli, the members of which could be separated by any chosen interval. The effective refractory period (ERP) was taken as the shortest interval between a pair of stimuli both of which yielded an action potential in at least 3 consecutive tests. The interval separating the upstrokes of 2 such action potentials was taken as the functional refractory period (FRP).

In vivo *experiments*

Rats were anaesthetized by subcutaneous injection of 2 to 3 ml of a 25% w/v solution of urethane and maintained at a rectal temperature of 37.5°C on a warmed operating table. A lead 2 electrocardiogram was recorded via subcutaneous needle electrodes and displayed on a dual channel scroll-type storage oscilloscope (Cardiostore SEM 431, made by S.E. Laboratories). A reference trace was stored on one channel while ongoing signals were displayed on the second channel. For accurate timing of events the electrocardiogram was digitized and stored in the transient store microprocessor (see above). Drugs were administered via the jugular vein and intermittent positive pressure ventilation was applied via a tracheal cannula. The tidal volume of the ventilation pump was adjusted to maintain arterial P_{CO_2} within the normal range.

Non-ischaemic hearts

A 10 cm length of saline-filled plastic tubing was advanced to the left ventricle via the right carotid artery. A fine platinum wire was guided through this tube until its tip protruded 1 mm within the heart and its position adjusted to make light contact with the endocardial surface as shown by an injury current recorded from the wire. A second platinum wire, plastic covered except at its inner end, was inserted via the diaphragm into the anterior mediastinum and advanced until its tip touched the pericardium in the vicinity of the cardiac apex. Electrical stimuli, each of 1 ms duration and of twice diastolic threshold, were delivered to the heart via these two electrodes, at a frequency of 6 Hz. Refractory periods were determined with paired stimuli. The shortest interval between members of a pair of stimuli which still elicited a pair of QRS complexes in the electrocardiogram in at least 3 consecutive tests was taken as the ERP. The interval separating the R waves of 2 such responses was taken as the FRP. Pairs of stimuli, the members of which were separated by an interval slightly (*circa* 5 ms) greater than the prevailing ERP often elicited short runs of ventricular tachycardia. These short, self-limiting paroxysms were considered by Kowey *et al.*, (1983) to represent a reliable prelude to more serious arrhythmias such as ventricular fibrillation, although contrary views have been expressed by Jaillon *et al.* (1980). By restricting the stimulus voltage to twice diastolic threshold ventricular fibrillation was totally avoided in the present experiments and electrical injury at the tip of the electrodes was minimized.

Coronary-occluded hearts

A left parasternal thoracotomy was performed, the ribs retracted and the pericardial sac opened. A braided silk suture of size 6/0, with round-bodied curved needle attached (Type W593 Mersilk, made by Ethicon), was placed beneath the left coronary artery where it emerges from behind and immediately to the left of the right ventricular outflow tract, adjacent to the left atrial border, as described by Selye *et al.* (1960). Therefore, occlusion was distal to the origin of the main septal branch in those hearts in which it arises from the left coronary artery (Halpern, 1957). The ligature was tightened through a snare consisting of a 3 cm length of thick-walled plastic tubing. In some experiments the snare was released after 8 min of occlusion in order to monitor the so-called reperfusion arrhythmias. Preliminary tests showed that substantially longer or shorter periods of occlusion produced fewer arrhythmias after release of the snare, in confirmation of the findings of Kane *et al.* (1984). The lead 2 electrocardiogram was recorded continuously for 30 min from the time of occlusion, using a magnetic-

tape cassette recorder (Medilog series 4–24, made by Oxford Medical). Tapes were replayed at the end of the experiment via a DDA2 analysis unit made by the same company.

Following coronary occlusion rat hearts displayed frequent, but usually short, self-limiting episodes of various ventricular tachyarrhythmias (VT). These paroxysms were characterized, at least initially, by rapidly repetitive QRS complexes of an abnormal and rapidly changing shape. Previous workers have referred to these arrhythmias by various names (Clark *et al.*, 1980; Marshall *et al.*, 1981; Johnston, *et al.*, 1983). However, there is widespread recognition that the nomenclature is unsatisfactory, the subject having been reviewed by Schweitzer & Mark (1983). At times the cardiac rhythm in the present experiments was unequivocal ventricular fibrillation, using the criteria of Schamroth (1971). At other times a designation of ventricular tachycardia was appropriate. These episodes frequently interconverted and intermediate forms, perhaps best termed ventricular flutter, were much in evidence. To avoid arbitrary and subjective distinctions the total time spent in these combined forms of VT (termed the VT duration) was simply noted.

Drugs used

Meobentine and bethanidine were gifts from Burroughs Wellcome Ltd., and quinidine was purchased from Sigma Co. Ltd. All doses and molar concentrations quoted in this paper refer to the sulphate salts. Molecular weights were:- quinidine sulphate 747; bethanidine sulphate 482; meobentine sulphate 512. The logarithm of the octanol:water partition coefficients measured at pH 7.4 were:- quinidine 3.6, bethanidine 2.8 and meobentine 2.5.

Results

In vitro *experiments*

The mean diastolic value of V_m measured in the basic superfusion medium was -82 mV ($\pm$ 10 mV), with an action potential duration measured to 90% repolarization (APD_{90}) of 61 ± 8 ms. Using paired stimuli, the FRP was found to be 42 ± 6 ms, corresponding to a V_m value at the point of earliest reexcitability of -68 ± 7 mV, which represents 83% repolarization (Table 1).

Addition of bethanidine or meobentine to the superfusate in final concentrations between 2 and 16 μM increased both APD_{90} and FRP, without causing a significant change in diastolic V_m (Table 1). Prolongation of FRP (ΔFRP) was usually significantly greater than the associated change in APD_{90} (ΔAPD_{90}), as shown in Table 1. This suggests that, in addition to slowing repolarization, and hence delaying the start of the restoration of excitability, both bethanidine and meobentine also slowed the return of full excitability after repolarization had taken place. This was most clearly seen during paired stimulation. The $\dot{V}_{max}$ value of the second action potential of a pair was plotted against the time interval (ΔT) between the point of attainment of 83% repolarization during the

Table 1 Effects of drugs on the electrical properties of rat isolated myocardium

Drug *Name*	*Concentration* (μM)	V_m (mV)	V_{max} (V s^{-1})	APD_{90} (ms)	*ERP* (ms)	*FRP* (ms)
Control	-	82 ± 10	192 ± 11	61 ± 8	38 ± 7	42 ± 6
Bethanidine	5	82 ± 9	205 ± 16	64 ± 10	39 ± 16	48 ± 11
Bethanidine	10	78 ± 10	202 ± 18	75 ± 6	73 ± 13*	81 ± 10*
Bethanidine	20	74 ± 12	184 ± 15	87 ± 6*	98 ± 20*	106 ± 15*
Meobentine	2	76 ± 11	193 ± 12	66 ± 9	45 ± 6	48 ± 9
Meobentine	4	73 ± 8	195 ± 18	68 ± 12	60 ± 11*	67 ± 14*
Meobentine	8	80 ± 12	186 ± 19	89 ± 5*	74 ± 12*	92 ± 18*
Meobentine	16	73 ± 13	187 ± 24	97 ± 8*	116 ± 23*	130 ± 26*
Quinidine	4	75 ± 7	189 ± 9	62 ± 7	40 ± 14	45 ± 11
Quinidine	8	84 ± 10	180 ± 21	70 ± 8	64 ± 10*	77 ± 18*
Quinidine	16	72 ± 12	181 ± 25	98 ± 10*	105 ± 19*	123 ± 33*

Each value is the mean of between 20 and 54 observations ± s.e. All observations were made after exposure to the drug for 1 h, by which time drug-effects were near to maximum. *Significantly different (Student's *t* test, $P < 0.05$) from the control value.

Abbreviations used: V_m, transmembrane potential; V_{max}, maximum rate of change of V_m; APD_{90}, action potential duration measured to 90% repolarization; ERP, effective refractory period; FRP, functional refractory period.

first action potential and the start of phase 0 of the second action potential. This yielded an approximately exponential relationship from which the time constant (TC) for recovery of excitability was calculated (Figure 1). The value of ΔT was always measured from the point of 83% repolarization in the first action potential, irrespective of whether the tissue had actually become re-excitable by this time. Bethanidine and meobentine caused concentration-dependent prolongations of the TC for recovery of membrane excitability. The concentrations of meobentine and of bethanidine needed to double the value of TC obtained under drug-free conditions were 8.8 and 7.5 μM respectively.

The concentration of KCl in the superfusate exerted a considerable influence on some, but not all, of the measured effects of meobentine, as shown in Figure 2. Raising the concentration of KCl from 2.5 to 10 mM greatly potentiated the drug-induced prolongation of FRP, but had no statistically significant effect upon the drug-induced prolongation of APD_{90}. The response to bethanidine was influenced by KCl concentration in a similar way.

In most respects the actions of quinidine resembled those of bethanidine and meobentine, as shown in Table 1. However, compared with bethanidine and meobentine the rates of onset and offset of action of quinidine were faster (Figure 3). Another difference was that the action of quinidine was only slightly potentiated by raising the KCl concentration, in confirmation of previous findings (Northover, 1983). The majority of the experiments in this study were conducted at a stimulation rate of 1 Hz. Experiments conducted at a rate of 4 Hz, the normal heart rate of the rat, showed that there was no significant difference in APD_{90} between tissues paced at 1 Hz and at 4 Hz. In addition, the prolongation of APD_{90} produced by quinidine at 16 μM was not significantly different at the 2 rates of stimulation.

Ventricular muscle subjected to paired stimuli, the second member of which fell within 5 ms of the end of the ERP caused by the first, showed brief paroxysms of between 3 and 30 consecutive spontaneous action potentials in 82% of tests conducted in the normal superfusate. In contrast, this phenomenon was a universal feature when the experiment was conducted in a superfusate containing 2.5 mM KCl and was never seen when the KCl concentration was raised to 10mM. When meobentine, bethanidine or quinidine was added to the normal superfusate at a concentration sufficient to prolong the ERP by 50% or more, consecutive spontaneous action potentials were never seen.

In vivo *experiments*

Non-ischaemic hearts

Using paired stimuli, and in the absence of an antiarrhythmic drug, the ventricular ERP and FRP were found to be 52 ± 8 ms and 61 ± 10 ms, respectively.

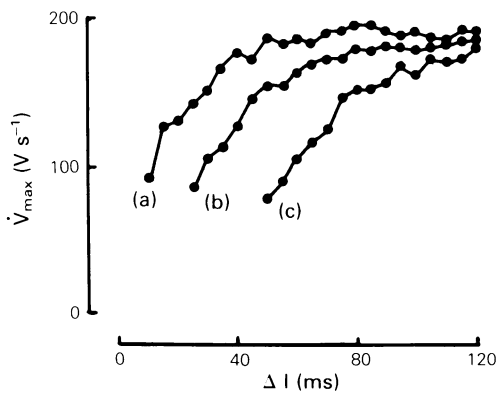

Figure 1 Electrical responses of rat isolated myocardium to paired stimuli, the second member of which was timed to produce an action potential during phase 3 of the action potential caused by the first. The phase 0 V_{max} values were derived from variously timed (ΔT) second responses in the absence of drug (a), and in the presence of meobentine at 8 μM (b) and at 16 μM (c).

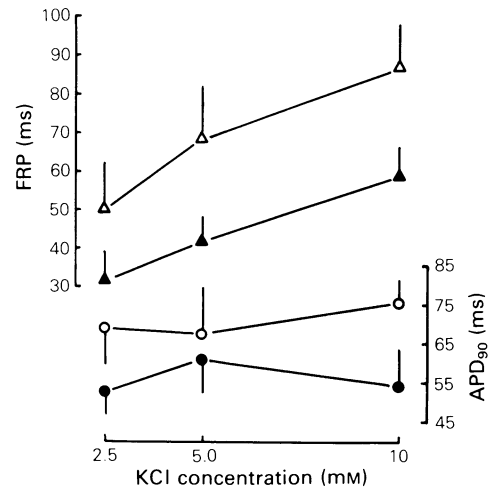

Figure 2 Changes in action potential duration measured to 90% repolarization (APD_{90}; circles) and functional refractory period (FRP; triangles) produced by exposure of the myocardium *in vitro* for 1 h to various concentrations of KCl, with (open symbols) or without (closed symbols) the addition of meobentine 4 μM. Data points are the means of between 25 and 46 observations. Vertical lines represent s.e.

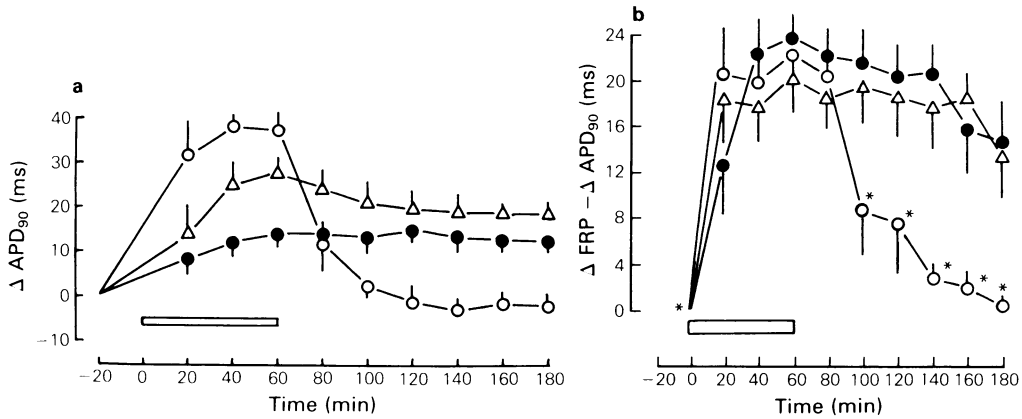

Figure 3 Time course of onset and offset of action of quinidine (16 μM; ○), meobentine (8 μM; △) and bethanidine (10 μM; ●) applied *in vitro* for 60 min, starting at time zero, as indicated by the horizontal bar. Changes in action potential duration measured to 90% repolarization (APD_{90}) (a) and in the difference between functional refractory period (FRP) and APD_{90} (b) were calculated with reference to values obtained in drug-free superfusate. Data points represent means of between 20 and 54 observations. Vertical lines represent s.e. An asterisk denotes that spontaneous consecutive action potentials were elicited in at least 10% of tests where a second stimulus was applied 5 ms beyond the end of the effective refractory period (ERP) of a previous action potential.

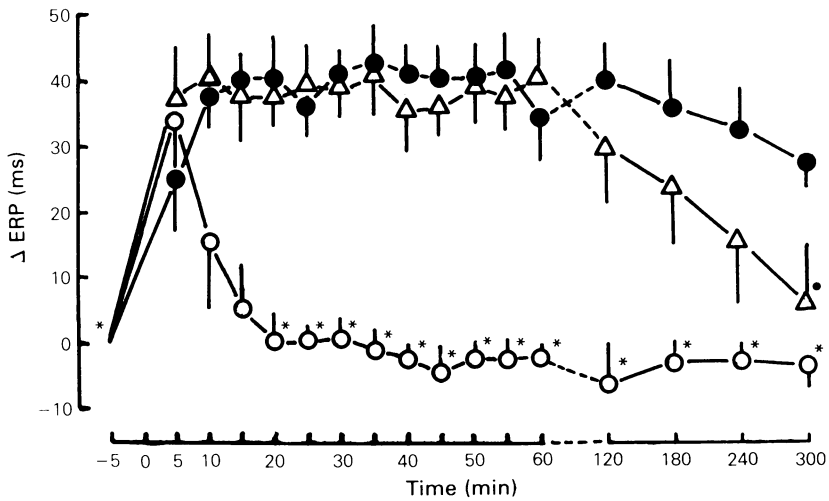

Figure 4 Changes in effective refractory period (ΔERP) caused by bolus doses of quinidine (20 mg kg^{-1}; ○), bethanidine (20 mg kg^{-1}; ●) or meobentine (10 mg kg^{-1}; △) given intravenously at time zero. An asterisk denotes that ventricular tachycardia was elicited in at least 10% of tests by stimuli applied 5 ms beyond the end of the ERP of a preceding heart beat. Data points represent means of between 18 and 37 observations from at least 4 animals. Vertical lines represent s.e.

Intravenous administration of bolus doses of bethanidine, meobentine or quinidine prolonged both ERP and FRP. Figure 4 shows that, in confirmation of its *in vitro* actions, quinidine had a briefer action that that of bethanidine or meobentine.

Before anti-arrhythmic drug administration a pair of stimuli separated by an interval 5 ms greater than the ERP elicited a short run of ventricular tachycardia in 68% of tests. Such episodes usually contained between 3 and 5 QRS complexes, and all eventually ended spontaneously. This arrhythmia was completely prevented by prior administration of bolus doses of bethanidine, meobentine or quinidine sufficient to prolong the ERP by 30% or more. The ability of these 3 drugs to prevent ventricular tachycardia waned in parallel with the restoration of normal values of ERP, as shown in Figure 4. Rats tolerated intravenous doses of quinidine and bethanidine of up to 20 mg kg^{-1} without apparent ill effect. This was the maximum dose studied. However, doses of meobentine greater than 15 mg kg^{-1} caused varying degrees of atrioventricular block.

Ischaemic hearts

Permanent coronary occlusion caused episodes of ventricular tachyarrhythmia (VT) to occur after a delay of between 4 and 7 min. These episodes usually continued intermittently thereafter for another 6 to 12 min. However, in 9% of animals classical and unremitting ventricular fibrillation occurred from which the animal died. All other animals in the non-drug-treatment group survived and were in sinus rhythm at the end of the 30 min observation period. At the end of the experiment the animal was killed and the heart examined under a dissecting microscope to verify the correct placement of the ligature.

Animals pretreated with bolus doses of bethanidine, meobentine or quinidine 6 min before occlusion showed a dose-related reduction of VT duration, as shown in Table 2. Animals pretreated with bethanidine or meobentine 60 min before occlusion were protected almost as well as those which received the drugs only 6 min before occlusion, whereas the protective effect of quinidine had diminished. Rats pretreated with these drugs 1 min after the onset of occlusion were less well protected against VT than those which were dosed just before occlusion (Table 2).

Rats subjected to 8 min of coronary occlusion, followed by reperfusion, developed a particularly severe form of VT, usually starting within a few seconds of release of the snare. In 71% of non-drug treated animals reperfusion evoked permanent ven-

Table 2 Effects of drugs on the duration of the ventricular tachyarrhythmia (VT) produced in response to coronary occlusion and reperfusion of the rat heart *in vivo*

Name	*Drug* *Dose* (mg kg^{-1})	(μM kg^{-1})	*Time† administered* (min)	*Duration of VT*(s) *Permanent occlusion* (0–30 min)	*Reperfusion‡* (8–30 min)
Control§	-	-	-	308 ± 28	1130 ± 215
Bethanidine	2	4.15	- 6	208 ± 23*	285 ± 43*
Bethanidine	2	4.15	- 60	190 ± 17*	270 ± 30*
Bethanidine	2	4.15	1	212 ± 29*	346 ± 52*
Bethanidine	20	41.5	- 6	0 *	14 ± 8*
Bethanidine	20	41.5	- 60	17 ± 8*	42 ± 16*
Bethanidine	20	41.5	1	24 ± 21*	23 ± 11*
Meobentine	1	1.95	- 6	123 ± 19*	319 ± 45*
Meobentine	1	1.95	- 60	107 ± 11*	331 ± 29*
Meobentine	1	1.95	1	154 ± 12*	405 ± 53*
Meobentine	10	19.5	- 6	14 ± 5*	10 ± 4*
Meobentine	10	19.5	-60	19 ± 15*	8 ± 5*
Meobentine	10	19.5	1	36 ± 12*	42 ± 19*
Quinidine	2	2.68	- 6	116 ± 15*	183 ± 27*
Quinidine	2	2.68	- 60	325 ± 24	1016 ± 192
Quinidine	2	2.68	1	114 ± 10*	315 ± 58*
Quinidine	20	26.8	- 6	6 ± 3*	0 *
Quinidine	20	26.8	- 60	286 ± 25	477 ± 114*
Quinidine	20	26.8	1	23 ± 13*	5 ± 5*

†Drugs administered before (negative sign) or after (positive sign) the start of occlusion, which was taken as time zero. ‡Reperfusion began 8 min after occlusion. §There were 12 permanently occluded control hearts and 16 reperfused control hearts, with between 7 and 10 animals in each drug-treatment group. Duration of VT quoted as mean ± se. An asterisk denotes a significant difference ($P < 0.05$) from control.

tricular fibrillation, ending fatally. Groups of rats pretreated 6 min before coronary occlusion with bethanidin, meobentine or quinidine in bolus doses of between 1 and 20 mg kg^{-1} were protected against reperfusion VT (Table 2). Rats given these drugs just after coronary occlusion were generally protected less well during the subsequent period of reperfusion than animals dosed before occlusion, as shown in Table 2.

Discussion

The 3 drugs chosen for the present study exerted effects on the rat heart which were similar in many respects. *In vitro*, for example, all 3 prolonged APD_{90}. Although previous workers have obtained broadly similar results some areas of disagreement can be found. These stem from the differences in the species of animal used, the part of the myocardium studied, the point during repolarization at which APD was measured and the frequency of stimulation employed. Meobentine, for example, was shown by Wang *et al.* (1977) to prolong APD_{100} of rat atrial muscle but to prolong only 'slightly' the APD_{100} of canine Purkinje fibres. In contrast, the APD_{50} of the canine Purkinje fibre was shortened by meobentine. Unfortunately, the rate of stimulation used for these experiments was not stated. Bethanidine was shown by Dangman *et al.* (1982) to have no effect upon the APD_{100} of canine Purkinje fibres stimulated at 1 Hz, despite the use of concentrations of drug of up to 80 μg ml^{-1}. At this concentration the rat myocardium is totally inexcitable to electrical stimulation. Clearly, therefore, large differences exist between species. For historical reasons, quinidine has been studied more thoroughly than probably any other anti-arrhythmic drug. Most investigators have found that quinidine prolongs APD (Vaughan Williams, 1958; West & Amory, 1960; Ducouret, 1976; Nawrath & Eckel, 1979; Nawrath, 1981; Nattel & Zeng, 1984). However, the magnitude of quinidine-induced prolongation of APD has been shown to depend upon experimental conditions. In the rabbit atrium, using a stimulation rate 10% above the natural, Vaughan Williams (1958) showed that there was no prolongation of APD_{50}, but only of the terminal portion of the action potential. West & Amory (1960), also using rabbit atrium, showed that quinidine prolonged both APD_{50} and APD_{90}, but this was only seen at stimulation rates of 4 Hz and less. In canine Purkinje fibres Nattel & Zeng (1984) found that the ability of quinidine to prolong APD_{95} was seen at stimulation rates between 0.2 Hz and 3 Hz, but the magnitude of the prolongation was much greater at rates below 1 Hz. In general, therefore, APD prolongation by quinidine is more prominent at low rates of stimulation but is still detectable at rates equal to the normal heart rate of the species concerned, provided that the APD includes the 'tail' of the action potential.

The ability of all 3 drugs studied in the present experiments to prolong refractory periods *in vitro* is another example of their similarity of action. Quinidine has been shown to prolong refractory periods *in vitro* by many workers, most of whom have also noted that the prolongation of refractory periods was considerably greater than could be accounted for solely by accompanying changes in APD (Vaughan Williams, 1958; Hoffman *et al.*, 1975; Ducouret,, 1976; Nawrath & Eckel, 1979; Nawrath, 1981; Northover, 1983). Meobentine was found by Wang *et al.* (1977) to prolong refractory periods in the rat myocardium *in vitro*, but the effects of bethanidine do not seem to have been described previously.

All 3 drugs used in the present experiments prolonged both ERP and FRP *in vivo*. In the case of quinidine this confirms previous findings in dogs (Wallace *et al.*, 1966; Duncan & Nash, 1972). Wallace *et al.* (1966) pointed out that the ability of quinidine to prolong myocardial refractory periods was readily demonstrated in the atria whereas in the ventricles of the conscious dog reflex changes in the autonomic control of the heart tended to obscure this effect unless the heart was denervated. Bethanidine, in oral doses of up to 30 mg kg^{-1}, has been found previously to prolong the refractory period of the human myocardium to a modest and variable extent (Benditt *et al.*, 1984). The statistical significance of these prolongations depended upon how the results were calculated. In the dog, on the other hand, bethanidine totally fails to change myocardial refractory periods *in vivo* after intravenous doses of up to 16 mg kg^{-1} (Patterson *et al.*, 1984). Michelson *et al.* (1981) demonstrated that meobentine prolonged canine myocardial refractory periods to a large extent, yet Zimmerman *et al.* (1984) in the same species and at the same dose of 20 mg kg^{-1} observed no effect. The discrepancy is unexplained. One is left with the impression that refractory period measurements *in vivo*, in contrast to those obtained *in vitro*, are liable to yield variable results, particularly in the dog. Rat hearts, on the other hand, seem to provide much more consistent results *in vivo*. However, one should remember that the action potential of the rat heart is atypical in shape. This makes it difficult to extrapolate from results obtained in the rat heart to other species, notably that of man.

Although the effects of the 3 drugs tested in the present experiments were qualitatively similar, their rates of onset and offset of action differed, with quinidine being more rapid than the others. This brevity of action of quinidine has been noted before (Klevans *et al.*, 1977). A marked persistence of effect, on the other hand, was observed by Wastila *et al.* (1981) with meobentine and by Leveque (1966) with bethanidine. This probably reflects the concentration of meobentine and bethanidine within the myocar-

dium (Touw *et al.*, 1977; Michelson *et al.*, 1981; Wastila *et al.*, 1981). Quinidine, on the other hand, is probably less concentrated in this way. Perhaps a little surprisingly, a protective effect against reperfusion arrhythmias was still detectable in the present experiments after a dose of quinidine of 20 mg kg^{-1} for up to an hour. Protection against the effects of permanent occlusion had disappeared by this time. The reason for the difference is unknown but warrants further investigation.

Occlusion of the left coronary artery, and more particularly the period immediately following occlusion, is associated with intense ventricular arrhythmia in the rat. Pretreatment with bethanidine, meobentine or quinidine reduced the duration of these arrhythmias in the present experiments. Previous workers have shown that quinidine protects against various ischaemia-induced arrhythmias in the rat heart (Kane *et al.*, 1981; Bergey *et al.*, 1982; Johnston *et al.*, 1983), the dog heart (Stephenson *et al.*, 1960; Bergey *et al.*, 1982) and the pig heart (Bergey *et al.*, 1982). Although bethanidine has been found to protect recently infarcted myocardium against certain electrically-induced arrhythmias (see Introduction), the effect against spontaneous arrhythmias occurring in the recently infarcted heart does not seem to have been demonstrated before. Meobentine has been shown previously to inhibit spontaneous post-coronary occlusion arrhythmias in both rats and dogs (Touw *et al.*, 1977; Wastila *et al.*, 1981). The ability of meobentine to suppress electrically-induced ventricular arrhythmias has been demonstrated previously for dogs, not only with a normal myocardium (Wastila *et al.*, 1981) but also in those with a recent infarction (Michelson *et al.*, 1981). However, the effectiveness of meobentine against ventricular arrhythmias induced electrically in the dog heart depends upon the nature and magnitude of the electrical stimulus used and upon the extent, the age, and the location of the infarcted tissue present (Zimmerman *et al.*, 1984). Unfortunately, it is impossible to decide which, if any, of the commonly used models of ischaemic heart disease mirrors the natural disease of man.

Shortly after the myocardium is reperfused following a period of ischaemia, ventricular arrhythmias are prominent. Not only is this true in man (Timmis *et al.*, 1982; Goldberg *et al.*, 1983a, b), but also in many experimental animals (Kane *et al.*, 1984; Manning & Hearse, 1984). All 3 drugs tested in the present experiments suppressed reperfusion arrhythmias in the rat. Quinidine was found previously to exert this effect not only in rats but also in dogs and pigs (Bergey *et al.*, 1982). There does not seem to be a previous study of the activity of bethanidine in this situation, but Wastila *et al.* (1981) showed that meobentine suppressed reperfusion arrhythmias in the dog.

In conclusion, the present experiments indicate that in the rat heart, both *in vivo* and *in vitro*, quinidine, bethanidine and meobentine have qualitatively similar actions. The most prominent of these are the prolongation of APD_{90} and the slowing of the return of full diastolic $\dot{V}_{max}$ after repolarization has taken place, causing a prolongation of ERP and FRP. Also, the three drugs protect the rat heart against ventricular arrhythmias produced by occlusion, either permanently or temporarily, of the left coronary artery.

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