Electrophysiological effects of bepridil and its quaternary derivative CERM 11888 in closed chest anaesthetized dogs: a comparison with verapamil and diltiazem

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1 The electrophysiological effects of bepridil, its quaternary derivative, CERM 11888 (methyl-pyrrolidinium bromide) (both 2.5 mg kg^{-1} i.v.) and those of verapamil and diltiazem (0.2 mg kg^{-1} i.v.) were studied in closed chest anaesthetized dogs at doses used in clinical studies.

2 The four drugs caused a bradycardia with the following order of potency: bepridil > CERM 11888 > diltiazem > verapamil.

3 All the compounds slowed conduction in the AV node, increased the refractory period (RP) and decreased Wenckebach rates with the following order: verapamil $\gg$ diltiazem > bepridil > CERM 11888.

4 Verapamil and diltiazem did not affect conduction or the RP in atria while bepridil weakly slowed the former and markedly increased the latter. CERM 11888 caused a lengthening of RP but this was a delayed effect.

5 In the ventricle, bepridil and CERM 11888 caused a small increase in the QRS and a more pronounced increase in the RP. Both compounds increased QTc but did not modify HV. Verapamil and diltiazem had no significant effects at the ventricular level.

6 Our results confirm that the main sites of action of calcium antagonists are the SA and AV nodes. Bepridil has a broader spectrum of activity and also acts at the atrial and ventricular levels. A comparison of the effects of bepridil with those of its quaternary derivative suggests the involvement of an intracellular action in the electrophysiological effects of bepridil.

Introduction

Bepridil is an antianginal drug (Cosnier *et al.*, 1977; Alpert *et al.*, 1985) having a long plasma half-life (Benet, 1985) which should allow it to be effective as a once-a day monotherapy for stable angina pectoris (Sharma *et al.*, 1988). In addition to the common property of calcium antagonists to inhibit the slow calcium current, bepridil also inhibits sodium channels (Schwartz *et al.*, 1985; Sperelakis, 1987). The combination of these two effects may explain its additional antiarrhythmic properties in animal experiments (Marshall *et al.*, 1984; Flaim & Cummings, 1986) and its efficacy against both supra-ventricular (Rowland *et al.*, 1985) and ventricular (Levy *et al.*, 1984) arrhythmias in man. However, bepridil also enters cells (Sperelakis, 1987) and is able to modulate intracellular calcium movements,

even in intact tissues (Lynch *et al.*, 1985a,b; 1986; Leboeuf *et al.*, 1987; 1988). In the present study, we have determined if such intracellular actions of bepridil could be involved in its electrophysiological effects in closed-chest anaesthetized dogs, by comparing the effects of bepridil with those of its quaternary derivative (methyl-pyrrolidinium bromide) CERM 11888. CERM 11888 would be expected to penetrate into cells to a lesser extent or at a much reduced rate than the parent drug bepridil. CERM 11888 has been shown to have an approximately similar potency to bepridil on sarcolemmal calcium and sodium channels (Wahler *et al.*, 1986; Schaeffer *et al.*, 1986; Leboeuf *et al.*, unpublished results). Thus in the present study the effects of bepridil and CERM 11888 were compared to those of two classical calcium antagonist drugs: verapamil and diltiazem (see Figure 1, for the different chemical

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Figure 1 Chemical structures of bepridil and its quaternary derivative CERM 11888 and of verapamil and diltiazem.

structures of these compounds) at doses used in clinical studies and for which comparative haemodynamic data exist in anaesthetized dogs (see Ponsonnaille *et al.*, 1982; Beaughard *et al.*, 1986).

Methods

Forty beagle dogs of either sex (12 to 16 kg) were anaesthetized with alpha chloralose (100 mg kg^{-1} i.v.) and sodium pentobarbitone (5 mg kg^{-1} i.v.). The trachea was cannulated and the animal respired with room air by means of a Minerve respirator. An electrocardiogram (ECG, Lead II) was recorded by use of subcutaneous electrodes. Three endocavitary electrodes (Plastimed 6 F) were positioned with the aid of an image intensifier. The first, a bipolar electrode, was positioned via the left femoral artery in the root of aorta at the level of the aortic cusps to record His-bundle electrogram (Scherlag *et al.*, 1968). The second, a quadripolar electrode, was positioned in the right atrium via the right jugular vein and used for atrial pacing and endocavitary recording of the atrial electrogram. The third electrode (bipolar) was placed in the right ventricle (via left femoral vein) for ventricular pacing. Blood pressure was measured with a Bell and Howell pressure transducer connected to the right femoral artery. Blood gases (P_{O_2} , P_{CO_2}) and pH were determined with an automatic analyser (Corning) and respiration was adjusted to obtain arterial blood gases (P_{O_2} 80–100 mmHg, P_{CO_2} 35–40 mmHg) and pH (7.4 ± 0.5) within the physiological range. Records were made on a four-channel recorder (Beckman R 511 A) at a paper speed of either 200 mm s^{-1} for determining the different intervals of conduction or 100 mm s^{-1} for refractory period determination.

Parameters studied

Heart rate, systolic (SAP) and diastolic (DAP) arterial pressure were assessed at baseline (Time 0) and 1, 5, 20, 35 and 50 min after the beginning of the infusion. The other electrophysiological parameters were measured at Time 0 and 5, 20, 35 and 50 min post-infusion. Interventricular conduction time (QRS) and repolarization (QT) were measured during spontaneous sinus rate. QTc was calculated by use of Bazett's formula ($QT/\sqrt{RR}$ Bazett, 1920) although, even in man, its ability to predict accurately the effects of drugs on repolarization is limited, particularly at low and high heart rates (Milne *et al.*, 1980; Rickards & Norman, 1981; Staniforth, 1983). Nevertheless it was felt justified to calculate QTc in this way, avoiding the 1 min post-drug time point when very often reflex tachycardia was evident, since it is a parameter frequently quoted

in pharmacological and clinical studies (see Brugada *et al.*, 1988; Zehender *et al.*, 1989). Furthermore under the present experimental conditions and when using a fixed pacing rate it was not always possible to measure QT because the stimulus artifact often arrived before the end of the T wave in cases where QT was lengthened by drugs. Finally the fact that the baseline sinus rates were similar in the different groups of animals used in these studies lends a better predictive value to these QTc measurements. The sinus recovery time (SRT), intraauricular (St-A), intranodal (AH) and His-Purkinje (HV) conduction times and atrial, AV node and ventricular refractory periods were determined during either fixed atrial or ventricular pacing (20% above the baseline spontaneous sinus rate). SRT was assessed during atrial pacing (during a 1 min period) using the atrial electrogram and was defined as the interval between the last auricular response elicited by stimulation and the first spontaneous one. The corrected SRT was measured according to the method of Narula *et al.* (1972) as the difference between the sinus pause duration and the spontaneous cycle length. The refractory periods of the atrium, AV node and ventricle were measured according to the extra-stimulus technique during atrial or ventricular pacing. After every 8th paced beat induced by stimulus S_1 , an extrastimulus (S_2) with the same intensity ($2 \times$ threshold) and duration (2 ms) was delivered by a stimulator (Medtronic 5325) at a decreasing S_1 - S_2 interval (at 10 ms steps) until S_2 no longer evoked a propagated response (R_2). There was a 3 s interval between each successive step. The effective refractory period (ERP) was defined as the greatest S_1 - S_2 interval not followed by an R_2 . The functional refractory period (FRP) was the smallest value of R_1 R_2 for any S_1 S_2 . For the AV junctional refractory periods the reference was the atrial R_1 - R_2 interval rather than S_1 - S_2 interval. Anterograde and retrograde Wenckebach rates were determined under atrial and ventricular pacing, respectively, by increasing progressively the rate of pacing until AV conduction block appeared.

Protocol

Dogs were divided into five groups (A, B, C, D, E) each of eight animals. Each group received a single drug concentration in a 10 ml volume injected over 1 min. Similar sequences of events were performed before and after drug application. First, without pacing, spontaneous sinus rate, QRS, QT and SAP and DAP were determined followed by a 1 min atrial pacing to obtain paced AH and HV, A-St and, at the end of pacing, SRT. Then, under similar conditions, atrial effective and functional refractory periods were determined (A-ERP, A-FRP respectively) followed

by the assessment of anterograde Wenckebach rate (A-Wck). At this time, ventricular pacing permitted measurement of ventricular effective and functional refractory periods (V-ERP and V-FRP respectively) followed by the retrograde Wenckebach rate (R-Wck).

Group A received physiological saline, group B: bepridil (2.5 mg kg^{-1}), group C: CERM 11888 (2.5 mg kg^{-1}), group D: verapamil (0.2 mg kg^{-1}) and group E: diltiazem (0.2 mg kg^{-1}). The doses of bepridil, verapamil and diltiazem are the mean doses commonly used in intravenous studies in man (Singh *et al.*, 1985a).

Drugs used

Bepridil monohydrochloride, monohydrate and CERM 11888, methyl pyrolidinium bromide salt were synthesized in the Department of Chemistry RL-CERM. Verapamil (base) was purchased as Isoptine Injectable from Laboratoire Biosedra France and diltiazem hydrochloride from Sigma Laboratories. The required amount of verapamil was made up to 10 ml using a 0.9% NaCl solution (Iso-Physio, UVA) and bepridil, CERM 11888 and diltiazem were dissolved directly in 10 ml of the same solution.

Statistical analysis

Differences between the changes in the various parameters from baseline values induced by the drugs and those observed in the control group of dogs were analysed by use of Student's *t* test for independent series.

Results

In the control group of animals, no significant changes in the various electrophysiological parameters were seen throughout the entire experimental period and the mean changes of the parameters in the control group was around 5% with the exception of cSRT which showed relatively large changes with time (time 0 = $86 \pm 10 \text{ ms}$, 20 min = $115 \pm 21 \text{ ms}$, 50 min = $95 \pm 24 \text{ ms}$). Analysis of variance of this data showed that these changes were not significant ($P \approx 0.3487$).

Effects of compounds on blood pressure

Initial systolic blood pressures in the 5 groups of animals (A, B, C, D and E) used in these experiments were 157 ± 7 , 173 ± 7 , 143 ± 7 , 165 ± 6 , and $145 \pm 12 \text{ mmHg}$, respectively.

Figure 2 Time course of the effects of bepridil, CERM 11888, verapamil and diltiazem on sinus node function. Changes in spontaneous sinus rate (a), sinus recovery time (SRT) (b) and corrected sinus recovery time (cSRT) (c) with time (in min) caused by bepridil (■), CERM 11888 (●), verapamil (○) and diltiazem (▲). Bepridil and CERM 11888 were given at a dose of 2.5 mg kg^{-1} i.v. while verapamil and diltiazem were given at a dose of 0.2 mg kg^{-1} i.v. Abscissa scales represent time after the beginning of the 1 min infusion of the compounds. Note that the effect of bepridil on spontaneous sinus rate was rapid compared to the other compounds. Symbols are the same in all the other figures. * $P < 0.05$, compared to the control group of animals by Student's *t* test for independent series. Vertical lines represent s.e.mean.

Bepridil, CERM 11888, verapamil and diltiazem all caused a transient hypotension at the end of injection which returned to baseline values after 5 min for bepridil but required around 10 to 15 min

Figure 3 Time course of the effects of bepridil (■), CERM 11888 (●), verapamil (○) and diltiazem (▲) at the atrial level. Changes in intra-atrial conduction time (St.A) (a), atrial effective refractory period (A-ERP) (b) and atrial functional refractory period (A-FRP) (c) caused by the different compounds. Note that bepridil was the sole compound to have a marked effect on these parameters while the significant effect of CERM 11888 was delayed compared to it. * $P < 0.05$, compared to the control group of animals by Student's *t* test for independent series. Vertical lines represent s.e.mean.

for the other compounds. At time 1 min, SAP and DAP were lowered respectively by 10.5 and 23.5% by bepridil, 19 and 30% by CERM 11888, 17 and 28% by verapamil and 10 and 23% by diltiazem.

Effects of compounds on sinus node function

Baseline spontaneous sinus rates of groups A, B, C, D, E were 137 ± 9 , 141 ± 7 , 155 ± 6 , 139 ± 8 and 153 ± 7 beats min⁻¹ respectively. All compounds caused significant bradycardia (Figure 2a). However, the effect of bepridil was maximal after 5 min whilst

Figure 4 Time course of the effects of bepridil (■), CERM 11888 (●), verapamil (○) and diltiazem (▲) on AV node function. Changes in intranodal conduction time (AH) (a), anterograde Wenckebach rate (A-Wck) (b) and retrograde Wenckebach rate (R-Wck) (c) caused by the different compounds. Note that on these parameters verapamil was much more potent than the other compounds. * $P < 0.05$, compared to the control group of animals by Student's *t* test for independent series. Vertical lines represent s.e.mean.

that of the other compounds only appeared after 20 min. At 1 and 5 min, there was a significant difference between the effects of bepridil and those of its quaternary derivative which was the only drug to cause a significant, but transient, tachycardia at the end of infusion (see Figure 2a).

Bepridil, CERM 11888 and diltiazem lengthened SRT while verapamil did not significantly modify this parameter (Figure 2b). The effects of bepridil

Figure 5 Time course of the effects of bepridil (■), CERM 11888 (●), verapamil (○) and diltiazem (▲) at the ventricular level. Changes in His-Purkinje conduction time (HV) (a), ventricular effective refractory period (V-ERP) (b) and ventricular functional refractory period (V-FRP) (c) elicited by the different compounds. It should be noted that although the effects of bepridil, unlike that of CERM 11888, on V-ERP (5 min) reached statistical significance from control values, there was no significant difference between the effects of bepridil and CERM 11888 at this time point. * $P < 0.05$, compared to the control group of animals by Student's *t* test for independent series. Vertical lines represent s.e.mean.

and CERM 11888 were greater than those of diltiazem on this parameter and, as with the bradycardiac effect, that of CERM 11888 was delayed compared to bepridil. Only CERM 11888 significantly increased cSRT (Figure 2c).

Atrial actions of compounds

Bepridil slightly, but significantly, increased intra-auricular conduction time (Figure 3a) and markedly lengthened effective (Figure 3b) and functional (Figure 2c) refractory periods of the atria. CERM 11888 only slightly affected and diltiazem and verapamil had no significant effect on these parameters.

Effects of compounds on AV node function

Verapamil had a marked and long-lasting effect on atrioventricular conduction time (Figure 4a) while diltiazem and bepridil caused significant but less lengthening of AH at a fixed pacing rate. Again, compared to bepridil, the effects of CERM 11888 were delayed. The same potency order for the compounds was seen on antegrade (Figure 4b) and retrograde (Figure 4c) Wenckebach rates. Under these experimental conditions we rarely obtained the effective refractory period of the AV node because it was shorter than the atrial period. However, in the dogs where the baseline refractory period of the AV node was able to be determined, verapamil caused the most marked lengthening ($\approx +100$ ms) in this parameter while the effects of diltiazem and bepridil were about 50% of verapamil.

Ventricular actions of compounds

As shown in Figures 5 and 6, verapamil and diltiazem had no effects on the electrophysiological parameters of the ventricle. Bepridil and CERM 11888 slightly increased QRS interval (Figure 6a) and effective refractory period (Figure 5b), had no effect on HV interval (Figure 5a), lengthened QT (Figure 6b), QTc (Figure 6c) and the functional refractory period (Figure 5c); CERM 11888 had the longest duration of action.

Discussion

In the myocardium excitation is mediated by two major inward currents. In 'slow structures', such as the sinus and AV nodes, it is mediated mainly by a slow inward calcium current. In 'fast structures', such as the atria, ventricles and the His-Purkinje system, excitation is mediated by a fast inward sodium current (see Fleckenstein, 1985). In this study, we have shown that in good agreement with their relatively selective action on slow calcium channels (Fleckenstein, 1985; Singh *et al.*, 1985a; Sperelakis, 1987), verapamil and diltiazem at the dose levels used (0.2 mg kg^{-1} i.v.), only modified the rate of conduction and the refractory periods of the 'slow structures' and had no significant effects upon 'fast structures'. Thus both compounds elicited long-lasting bradycardia, markedly increased the intra-nodal conduction time (AH) and reduced antegrade and retrograde Wenckebach rates. The fact that verapamil was more active than diltiazem in these respects is probably explained by the fact that verapamil is somewhat more potent (2–3 times) than diltiazem as a calcium channel blocker *in vitro* (Lamar *et al.*, 1983; Zsoter & Church, 1983). These

Figure 6 Time course of the effects of bepridil (■), CERM 11888 (●), verapamil (○) and diltiazem (▲) on repolarization. Changes in interventricular conduction time QRS (a), QT (b) and corrected QT (c) values elicited by the compounds. There was no significant difference between the effects of bepridil and those of CERM 11888 on QRS. Note that only these two compounds significantly increased QT and QTc intervals. * $P < 0.05$, compared to the control group of animals by Student's *t* test for independent series. Vertical lines represent s.e.mean.

findings are similar to those found by other workers in the dog (Millard *et al.*, 1982; Singh *et al.*, 1982) and are probably related to their direct effects upon the sinus and AV nodes (Taira, 1979; Kawai *et al.*, 1981).

Similar effects on 'slow structures' have also been demonstrated with bepridil *in vivo* (Beaughard *et al.*, 1982; Kawada *et al.*, 1983) and, *in vitro* studies in cardiac muscle have shown that this compound preferentially inhibits slow calcium currents (Labrid *et al.*, 1979; Yatani *et al.*, 1986). Such an action could

explain the effect of bepridil on 'slow structures' observed in the present study. These experiments have also shown that the quaternary ammonium derivative of bepridil, CERM 11888, has effects upon 'slow structures' but these were somewhat weaker, and more delayed in onset, than those induced by bepridil. *In vitro* experiments have shown that CERM 11888 has an equivalent calcium channel blocking potency to bepridil (Wahler *et al.*, 1986; Schaeffer *et al.*, 1986), although recent results have indicated that CERM 11888 is some 2–3 times less potent than bepridil at vascular calcium channels (John and Massingham, unpublished results). Further experiments are required to resolve this discrepancy.

In addition to its effects upon slow calcium channels, it is well known that bepridil (Labrid *et al.*, 1979; Yatani *et al.*, 1986) and CERM 11888 (Leboeuf unpublished results) can also inhibit fast sodium channels at concentrations only slightly higher than those affecting the slow calcium channel. Our results also provide *in vivo* evidence that bepridil and CERM 11888 can act upon 'fast structures' to increase refractory periods in atria and ventricles and to slow atrial and intraventricular conduction times.

Comparison of the effects of bepridil and CERM 11888 on the slow action potential has suggested that they act at a common site on the slow calcium channel, probably at the exterior of the cell. Bepridil, however, may also possess a second site of action inside the cell, which may not be readily accessible to its quaternary derivative, CERM 11888 (see Wahler *et al.*, 1986). In the present experiments the effects of bepridil on sinus node, atrial refractory periods and AV node were more marked and significantly different from the effects of CERM 11888, which again suggests additional sites of action for the parent drug. Bepridil has been shown to enter readily and to accumulate in cells (Cramb & Dow, 1983; Pang & Sperelakis, 1983; 1984), whereas CERM 11888, being a charged molecule, would presumably enter cells less readily than the parent molecule. In agreement with this assumption, we have recently shown that bepridil, but not CERM 11888, decreased the amplitude of caffeine-induced contractions in ferret heart trabeculae *in vitro*, responses which are known to be mediated by the intracellular release of calcium from sarcoplasmic reticulum (SR) stores (Leboeuf *et al.*, 1987; Chapman & Tunstall, 1988). It is also interesting to note that the relative importance of calcium

release in the excitation-contraction coupling mechanism is much more important in atria than in the ventricle (Fabiato & Fabiato, 1978; Bers, 1985). An action of bepridil on calcium released from the SR might, in part, explain why in these experiments the electrophysiological effects of bepridil are more manifest on supraventricular compared to ventricular structures (see also Sassine *et al.*, 1984). A decreased intracellular release of calcium could modify the kinetics of sarcolemmal calcium channels, the amplitude of the calcium-activated K^+ current and Na^+-Ca^{2+} exchange (see Noble, 1984), which may lead to a lengthening of the action potential and an increase in the refractory period. Studies performed in rabbit heart have shown that bepridil causes a greater lengthening of atrial than ventricular action potentials (Winslow *et al.*, 1986). Thus an intracellular action may also be involved in the effects of bepridil on refractory periods and repolarization of the ventricle but these are weaker than the effects seen in atria perhaps, as suggested previously, because calcium-induced calcium release is less important in this structure. Finally, the effects of diltiazem, verapamil and bepridil in this closed-chest, anaesthetized dog model are very similar to those obtained with these compounds in the clinical situation (Ponsonnaille *et al.*, 1982; Singh *et al.*, 1985a,b) in agreement with findings of other workers (Brugada *et al.*, 1988). Thus, this model may be useful for the evaluation and extrapolation of the electrophysiological effects of cardioactive drugs to man.

In conclusion, these results have shown that bepridil has a broader electrophysiological profile than the classical calcium antagonists verapamil and diltiazem. In this respect bepridil is unique. Such properties could account for the activity of bepridil against both supraventricular and ventricular arrhythmias (Fauchier *et al.*, 1985; Levy *et al.*, 1984; Rowland *et al.*, 1985) in addition to its pronounced antianginal properties (Alpert *et al.*, 1985). Comparison of bepridil with its quaternary ammonium derivative, CERM 11888, indicated that intracellular effects, in addition to an action upon slow calcium and fast sodium channels, may be responsible for this unique pharmacological profile of bepridil.

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