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Electromechanical effects of bepridil on rabbit isolated hearts

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1 Electromechanical effects of a new antianginal agent, bepridil, on Langendorff-perfused rabbit hearts were compared with those of verapamil and lidocaine.

2 Bepridil at concentrations above 2×10^{-7}M caused a dose-related decrease in heart rate (HR), a prolongation of the atrio-His bundle conduction time (A-H interval) and a prolongation of the functional refractory period (FRP) of the atrioventricular (A-V) node. Similar changes in HR, A-H interval and the FRP of the A-V node were observed with verapamil at concentrations above 2×10^{-8}M. Lidocaine at above 4×10^{-5}M prolonged slightly the A-H interval and the FRP of the A-V node but did not decrease the HR.

3 Bepridil at concentrations above 10^{-6}M prolonged both the His bundle-ventricular conduction time (H-V interval) and the effective refractory period (ERP) of ventricular muscles. Similar changes in the H-V interval and in the ERP of ventricular muscles were observed with lidocaine at above 10^{-5}M. Verapamil ranging between 5×10^{-8}M and 8×10^{-7}M had no effect on the H-V interval and appreciably shortened the ERP of ventricular muscles.

4 Bepridil at concentrations above 2×10^{-6}M reduced the developed tension as did verapamil at above 10^{-7}M.

5 On a molar basis, the depressant effect of bepridil on HR and the A-V nodal conduction, which may reflect inhibitory action on the slow channels, was less than one tenth that of verapamil. Bepridil was more potent than lidocaine in prolonging the H-V interval and the ERP of ventricular muscles indicating a possible inhibition of the fast sodium channels. Both of these electrophysiological effects of bepridil may afford significant bases for the antiarrhythmic action of the drug.

Introduction

Previous studies of bepridil on the transmembrane action potential of ventricular muscles have indicated that bepridil inhibits both the fast and slow channels of cardiac muscles, and that the inhibitory action on the fast sodium channels is qualitatively similar to lidocaine in terms of its voltage and rate-dependency (Anno, Furuta, Itoh, Kodama, Toyama & Yamada, 1984). From these findings it is suggested that bepridil has characteristics similar to other Class Ib as well as Class IV anti-arrhythmic drugs currently available (Hausworth & Singh, 1979).

In the present experiments, the effects of bepridil on the electromechanical performance of the isolated Langendorff-perfused heart of the rabbit were investigated and compared with those of two reference drugs, lidocaine and verapamil, in order to clarify the pharmacological profile of bepridil as an antiarrhythmic agent more extensively. Based on the results obtained, the potential usefulness and possible side effects of the drug in the treatment of cardiac arrhythmias are also discussed.

Methods

Rabbits weighing 1.5 to 2.0 kg were killed by a blow on the head and exsanguinated through the carotid arteries. The heart was quickly removed and a cannula was inserted into the aorta for Langendorff perfusion. The preparation was perfused at a constant flow rate (20 ml min^{-1}) with Krebs-Ringer solution gassed with 95% O_2 and 5% CO_2 having the following

composition (mM): NaCl 120.3, KCl 5.0, $CaCl_2$ 1.2, $MgSO_4$ $7H_2O$ 1.3, NaH_2PO_4 1.2, $NaHCO_3$ 24.2 and glucose, 5.5 (pH 7.4). The temperature of the perfusate was maintained at 33 °C.

Bipolar stainless steel electrodes with an interpolar distance of 1.0 mm were inserted through a small incision made in the right atrium so as to record His-bundle electrograms (HBE). The signal was amplified at a frequency response from 100 to 500 Hz with a time constant of 0.03 s and displayed on a digital storage oscilloscope (Tektronix 5223) as well as registered on a pen recorder (Watanabe WR 3001). Two pairs of stimulating electrodes (interpolar distance, 1.0 mm) made of stainless wires were placed on the right atrium close to the sinus node region and on the anterior epicardial surface of the left ventricular free wall. A strain-gauge transducer (Nihon Kohden SB-1T) was connected to the apex of the heart in order to record the isometric tension. The resting tension was adjusted to the level where a maximal developed tension was obtained under control condition.

Parameters measured were as follows: spontaneous firing rate of the heart (HR), atrio-His bundle conduction time (A-H interval), His bundle-ventricular conduction time (H-V interval), functional refractory period (FRP) of the atrioventricular (A-V) node, effective refractory period (ERP) of ventricular muscles and the developed tension (DT). Atrioventricular conduction time and DT were measured under constant drive at a cycle length of 600 ms through stimulating electrodes on the right atrium. The pulses for stimulation were 2 ms in duration and twice the diastolic threshold in intensity. The A-H interval was defined from the onset of the first rapid atrial deflection (A) to the first rapid His bundle deflection (H) on HBE, and the H-V interval from H to the beginning of ventricular activity (V) (Figure 1). To obtain the FRP of the A-V node a premature stimulus (S_2) was applied through atrial stimulation electrodes with various coupling intervals at every tenth basic stimulus (S_1) at a cycle length of 600 ms using a programmable stimulator. The FRP of the A-V node was defined as the shortest interval between two successive His bundle deflections. The duration and the intensity of the premature pulse were the same as those for basic ones. A similar extrastimulus method was used to obtain the ERP of ventricular muscles. The tenth basic stimulus at a cycle length of 400 ms to the left ventricle was followed by a premature stimulus (S_2) at various coupling intervals, and the shortest S_1–S_2 interval cap-

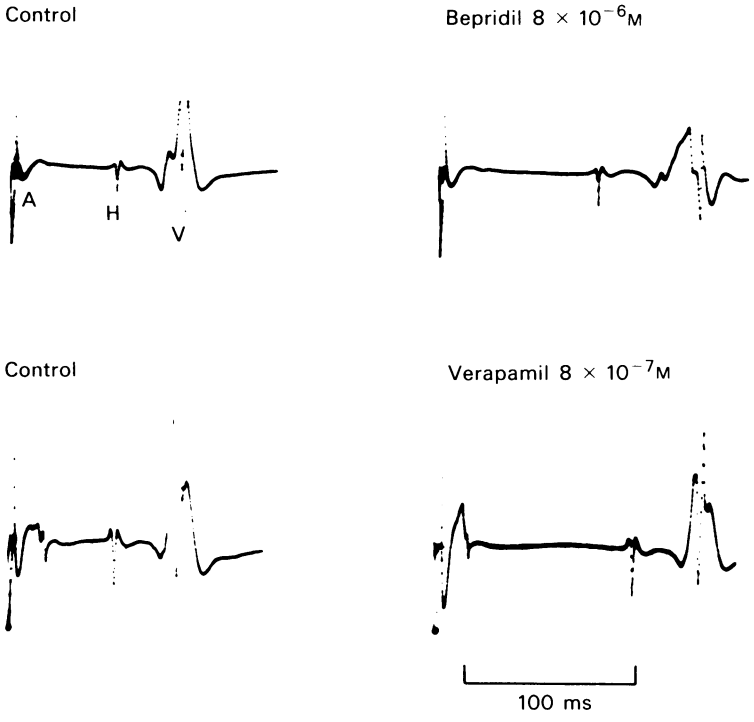

Figure 1 Effects of bepridil and verapamil on His bundle electrograms (HBE). The records were obtained before (control) and 15 min after application of bepridil (8×10^{-6}M) or verapamil (8×10^{-7} M). A: atrial deflection; H: His bundle deflection; V: ventricular deflection.

tured by ventricular responses was defined as ERP. The ventricular response was monitored by the electrogram obtained through a pair of bipolar electrodes placed 2.0 mm away from the stimulating electrodes.

Control measurements were performed after the equilibration period for 40 min. Then, action of drugs was measured 15 min after the hearts were perfused with the test solution containing one of the following three drugs: bepridil at a concentration ranging from 2×10^{-7}M to 2×10^{-5}M, verapamil from 2×10^{-8}M to 2×10^{-6}M and lidocaine from 2×10^{-6}M to 8×10^{-5}M.

Data obtained are presented as percentage changes from the control values and statistical comparisons were made using Student's *t* test.

Results

Heart rate (HR)

Effects of bepridil, verapamil and lidocaine on the heart rate (HR) were examined in each of five spontaneously beating hearts. The results obtained are summarized in Figure 2. The average value of HR in these 15 preparations under control conditions was 97 ± 8 beats min^{-1} (mean ± s.d.). Bepridil caused a dose-related decrease in HR at concentrations above 10^{-6}M. The percentage decrease in HR with the highest concentration of the drug (2×10^{-5}M) was 18.2%. Similar but much more potent negative chronotropic action was observed with verapamil at lower concentrations. With verapamil at 2×10^{-6}M,

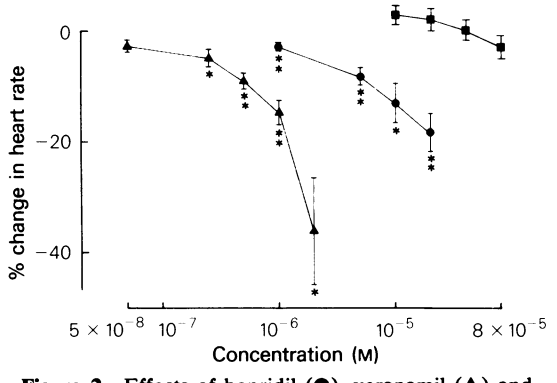

Figure 2 Effects of bepridil (●), verapamil (▲) and lidocaine (■) on the heart rate (HR). Ordinate scale shows percentage change from the control. Abscissa scale indicates the concentration of drug. Values presented are mean of five preparations for each drug with s.e. shown by vertical lines. Data were obtained 15 min after application of the drug at the respective concentrations. *Significantly different from the control at $P<0.05$. ** Significantly different from the control at $P<0.01$.

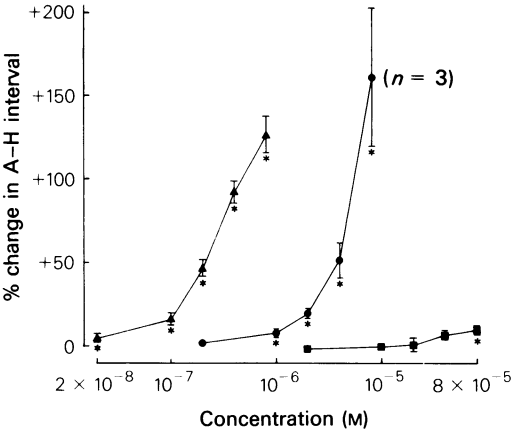

Figure 3 Effects of bepridil (●), verapamil (▲) and lidocaine (■) on the atrio-His bundle conduction time (A-H interval). Values presented are mean of five preparations for bepridil, five for verapamil, and six for lidocaine with s.e. shown by vertical lines. Data were obtained 15 min after application of the drug at the respective concentrations. Symbols are as in Figure 2.

abrupt reduction of HR to approximately half the initial value developed in two out of the five cases tested, suggesting the development of sinoatrial block. Lidocaine did not significantly affect HR even at the highest concentration used (8×10^{-5}M).

Atrio-His (A-H) interval and functional refractory period (FRP) of A-V node

Effects of the three drugs on atrio-His (A-H) interval were tested in each of five preparations. The average control value for the A-H interval in all 15 preparations was 53.2 ± 2.2 ms (mean ± s.d.). The results obtained are presented in Figures 1 and 3. Bepridil produced a dose-related increase in A-H interval at concentrations above 10^{-6}M. The percentage increase in A-H interval by the drug at 4×10^{-6}M, which did not produce A-H block, was about 50%. Bepridil at 8×10^{-6}M caused the A-H block of Wenckebach type in two out of the five preparations.

With verapamil, a significant prolongation of A-H interval was observed at a concentration of only 2×10^{-8}M. By increasing the dose of verapamil to 2×10^{-6}M, A-H block of the Wenckebach type developed in four out of five cases. The A-H prolongation by lidocaine was much less prominent than that induced by verapamil and bepridil, and was barely significant with the highest dose (8×10^{-5}M).

Changes in the functional refractory period (FRP) of the A-V node are presented in Figure 4. The average value of the A-V nodal FRP under control conditions in 15 preparations was 253 ± 26 ms (mean ± s.d.). Verapamil, bepridil and lidocaine, in

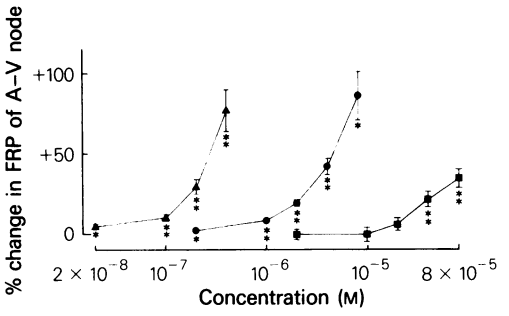

Figure 4 Effects of bepridil (●), verapamil (▲) and lidocaine (■) on the functional refractory period (FRP) of A-V node. Values presented are mean of five preparations for bepridil, five for verapamil and six for lidocaine with s.e. shown by vertical lines. Data were obtained 15 min after application of the drug at the respective concentrations. Symbols are as in Figure 2.

order of potency, produced a significant prolongation in this parameter. Thus, as with A-H interval changes, the effect of bepridil on the A-V nodal FRP was smaller than that of verapamil, and concentrations of bepridil ten times higher than those of verapamil were required for a comparable FRP prolongation.

His-ventricular (H-V) interval

The results obtained in five experiments for both bepridil and verapamil, and in six experiments for lidocaine, are summarized in Figure 5. The average control value for the H-V interval in all 16 preparations was 30.8 ± 1.2 ms (mean ± s.d.) Bepridil increased the H-V interval dose-dependently at concentrations above 10^{-6}M. The maximal prolongation was 26.4% at the highest concentration of the drug

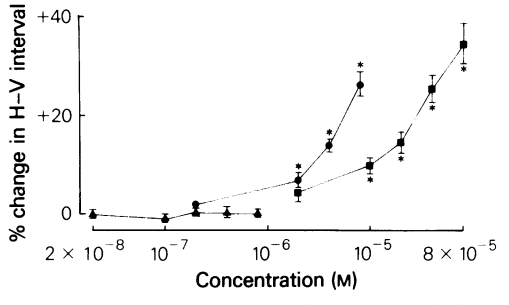

Figure 5 Effect of bepridil (●), verapamil (▲) and lidocaine (■) on the His-ventricular conduction time (H-V interval). Values presented are mean of five preparations for bepridil, five for verapamil and six for lidocaine with s.e. indicated by vertical lines. Data were obtained 15 min after application of the drug at the respective concentrations. Symbols are as in Figure 2.

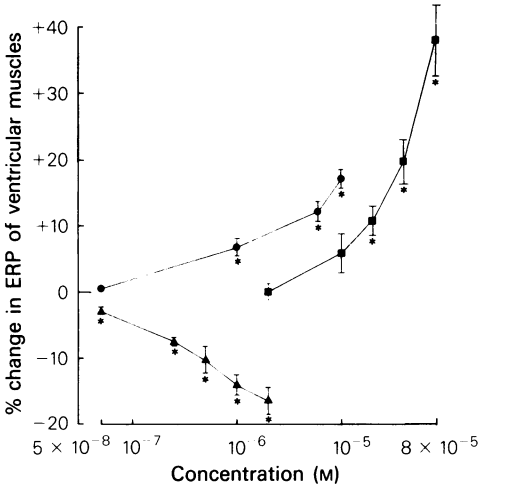

Figure 6 Effects of bepridil (●), verapamil (▲), and lidocaine (■) on the effective refractory period (ERP) of ventricular muscles. Values presented are mean of five preparations for bepridil, five for verapamil and six for lidocaine with s.e. indicated by vertical lines. Data were obtained 15 min after application of the drug at the respective concentrations. *Significantly different from control at $P<0.01$.

(8×10^{-6}M). A similar dose-dependent prolongation of the H-V interval was also observed with lidocaine at concentrations above 10^{-5}M. On the other hand, verapamil had virtually no effects on the H-V interval even at the highest concentration used (8×10^{-7}M).

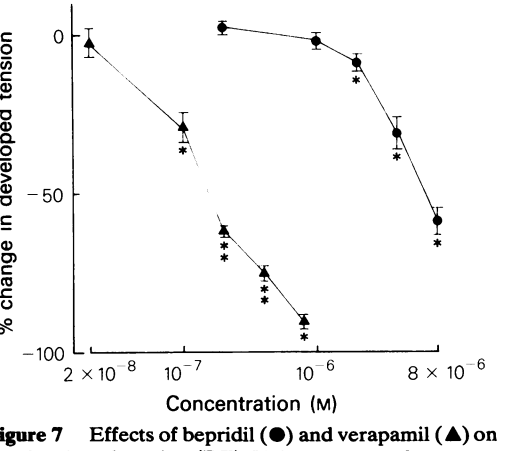

Figure 7 Effects of bepridil (●) and verapamil (▲) on the developed tension (DT). Values presented are mean of five preparations for both bepridil and verapamil. Data were obtained 15 min after application of the drug at the respective concentrations. Symbols are as in Figure 2.

Effective refractory period (ERP) of ventricular muscles

Effects of the three drugs on the ERP of the ventricular muscles in 16 experiments (five hearts for both bepridil and verapamil and six for lidocaine) are illustrated in Figure 6. The average control value of ERP in the 16 experiments was 221 ± 13 ms (mean $\pm$ s.d.). Bepridil and lidocaine prolonged the ERP of ventricular muscles dose-dependently at concentrations above 10^{-6}M and 2×10^{-5}M respectively. The mean increase in the ERP at the highest concentration of bepridil (10^{-5}M) was 16.8%.

When the hearts were treated with bepridil at 2×10^{-5}M, ventricular fibrillation was frequently induced by a single extrastimulus used to measure ERP, and it became very difficult to perform this procedure.

As to lidocaine, the average increase in ERP with the highest concentration of the drug (8×10^{-5}M) was 38.6%. In contrast to these drugs, verapamil caused a dose-related shortening of the ERP in ventricular muscles at concentrations above 5×10^{-8}M. Verapamil at 10^{-6}M produced an average shortening of the ERP of 14.1%.

Developed tension (DT)

Effects of bepridil and verapamil on the developed tension (DT) were examined in each of five preparations which were driven constantly at a cycle length of 600 ms. The results obtained are summarized in Figure 7. These two drugs caused a dose-dependent decrease in DT, although the intensity of their negative inotropic effect was quite different. The threshold concentrations for the decrease in DT were 2×10^{-6}M for bepridil, and 10^{-7}M for verapamil. The average decrease in DT induced by the highest concentration of bepridil (8×10^{-6}M) was -59.0%. This percentage decrease corresponded approximately to the reduction of DT with verapamil at 2×10^{-7}M.

Discussion

The results show that bepridil at concentrations above 2×10^{-7}M causes dose-related decreases in heart rate (HR), and prolongation of the atrio-His (A-H) interval as well as the functional refractory period (FRP) of the A-V node. These findings are consistent with previous *in vitro* and *in vivo* studies indicating the inhibitory action of bepridil on the pacemaker activity of sinus nodes (Cosnier, Duchene-Marullaz, Rispat & Streichenberger, 1977; Beaughard, Ferrier, Labrid, Lamar, Leboeuf & Piaris, 1982; Kane, Berdeja Garcia, Sanchez-Perez & Pastelin, 1983) and on the conductivity of A-V nodes (Chassaing, Moins & Lavarenne, 1977; Vogel, Crampton & Sperelakis, 1979). Since the electrical activity of sinus and A-V nodes depends primarily on the slow Ca^{2+} and/or Na^{+} inward currents (Irisawa, 1978; Carmeliet & Vereecke, 1979; Mendez, 1982), the negative chronotropic and the negative dromotropic effects of bepridil are most likely explained by its inhibitory action on the slow channels in the cardiac cell membrane (Vogel *et al.*, 1979; Labrid, Grosset, Dureng, Mironneau & Duchene-Marullaz, 1979). Verapamil, a well known cardiac slow channel blocker (Rosen, Wit & Hoffman, 1975), showed qualitatively similar changes to bepridil in HR, A-H interval and FRP of A-V node, but its effective concentrations were much lower than those for bepridil. The relative potency of bepridil to verapamil, which was calculated by the parallel line assay in dose-response curves on a molar basis, was 0.04 to 0.09 (Table 1).

Bepridil at above 10^{-6}M caused, like verapamil, a dose-dependent decrease in the developed tension (DT). The relative potency of bepridil compared with verapamil in producing the negative inotropic effect was 0.06 (Table 1). This finding is concordant with the facts described above, and may suggest that the potency of bepridil as a cardiac slow channel blocker is less than one tenth that of verapamil.

Table 1 Relative potency of bepridil to verapamil and lidocaine

	Bepridil	*Verapamil*	*Lidocaine*
Heart rate	0.09	1	—
A-H interval	0.06	1	—
FRP of AVN	0.04	1	—
Developed Tension	0.06	1	—
H-V interval	16.2	—	1
ERP of VM	7.9	—	1

Values were obtained by parallel line assay in the dose-response curves on a molar basis. FRP: functional refractory period; AVN: atrio-ventricular node; ERP: effective refractory period; VM: ventricular muscles.

Our data demonstrated that the His-ventricular (H-V) interval was also prolonged by bepridil at concentrations above 10^{-6}M. This may be attributed to the inhibitory action of bepridil on the fast sodium channels of the specialized conducting system in the ventricle. Bepridil at concentrations above 5×10^{-6}M caused a significant decrease in the maximum upstroke velocity ($\dot{V}_{max}$) of action potentials in guinea-pig ventricular muscles when the preparation was stimulated at a cycle length of 1.0 s, and such an inhibitory effect of bepridil on $\dot{V}_{max}$ was augmented at a higher stimulation frequency (Anno *et al.*, 1984). In the present experiment, the rabbit hearts were stimulated at a cycle length of 600 ms. Therefore, it is reasonable to assume that bepridil even at 10^{-6}M would have caused a considerable decrease in $\dot{V}_{max}$ of action potentials, which is enough to reduce the conduction velocity in Purkinje and ventricular muscle fibres.

Lidocaine at concentrations above 10^{-5}M caused a dose-dependent prolongation of H-V interval similar to bepridil, while it did not affect the A-H interval except at the highest concentration used (8×10^{-5}M). This lidocaine-induced H-V prolongation may also be explained by the drug's inhibitory action on the fast sodium channels. Previous reports (Hondeghem & Katzung, 1980; Bean, Cohen & Tsien, 1982; Campbell, 1983; (Anno *et al.*, 1984) have shown that lidocaine at above 10^{-5}M decreases $\dot{V}_{max}$ of action potentials in Purkinje as well as in ventricular muscle fibres especially when the tissues were stimulated at a cycle length shorter than 1.0 s. The relative potency of bepridil to lidocaine in its effect on H-V prolongation was 16.2 (Table 1).

In contrast to bepridil and lidocaine, verapamil did not prolong the H-V interval. This might be due to the relatively low concentrations of the drug. Verapamil was reported to decrease $\dot{V}_{max}$ of action potentials in Purkinje and ventricular muscle fibres at concentrations above $4 \sim 6 \times 10^{-6}$M (Rosen, Ilvento, Gelband & Merker, 1974; Hirata, Kodama, Iwamura, Shimizu, Toyama & Yamada, 1979). However, we did not use such high concentrations of verapamil in the experiments to measure the H-V interval because they always caused advanced A-H block.

In the present experiments, bepridil at above 10^{-6}M and lidocaine at above 2×10^{-5}M caused a dose-dependent prolongation of the effective refractory period (ERP) in ventricular muscles. On the other hand, as shown by us (Anno *et al.*, 1984) and the report by Vogel *et al.*, (1979), bepridil has negligible effects on the action potential duration (APD) of ventricular muscles or slightly shortens it. Lidocaine is also known to shorten APD of ventricular muscles (Singh & Hauswirth, 1974; Rosen, Hoffman & Wit, 1975). Accordingly, the prolongation of ERP by bepridil or lidocaine cannot be attributed to the lengthening of APD. Instead, it may probably be explained by a lengthening in the time-dependent refractoriness. In another paper, we have shown (Anno *et al.*, 1984) that bepridil, like lidocaine, causes a marked delay in the recovery kinetics of $\dot{V}_{max}$ during the diastolic intervals of several hundred milliseconds. As a consequence, premature stimuli at or near the end of repolarization will have a very slow upstroke velocity which would be insufficient to propagate the action potential to the surrounding myocardium. Recently, Campbell (1983) reported that lidocaine and mexiletine at high concentrations caused a marked prolongation of ERP in ventricular muscles through such a mechanism, despite their shortening or negligible effects on APD.

In the preparation treated with bepridil at 2×10^{-5}M ventricular fibrillation was easily induced by a single extrastimulus used to measure the ERP. This finding suggests that bepridil could be arrhythmogenic at toxic doses. Bepridil at such a high concentration might cause a slow conduction in the ventricle accompanied by a spatial inhomogeneity of refractoriness, which is an important prerequisite for the re-entrant arrhythmias precipitating ventricular fibrillation (Han & Moe, 1964; Marix, Yoon & Han, 1977). However, there is no evidence supporting this possible mechanism for the arrhythmogenic action of bepridil, and it is beyond the scope of this paper to extend the discussion in this direction.

Verapamil and D-600 in their racemic forms were reported to have dual inhibitory effects on both the fast and the slow channels of cardiac cells especially at high concentrations (Bayer, Kalusche Kaufmann & Mannhold 1975). In this respect, bepridil seems similar to these drugs. However, with verapamil and D-600, the threshold concentration for the development of fast channel inhibition are 20 to 100 times higher than those for slow channel inhibition (Rosen *et al.*, 1974; 1975; Wit & Cranefield, 1974; Bayer *et al.*, 1975; Hirata *et al.*, 1979). Therefore, the former effect is considered to be negligible within the therapeutic concentration range (Singh & Mandel, 1980). In contrast, as shown in the present study, most of the cardiac effects of bepridil reflecting the inhibitory action on both the fast and the slow channels were observed at concentrations above 10^{-6}M, which is well within the clinically detected plasma level (unpublished data). Accordingly, bepridil is expected to exert anti-arrhythmic actions through the combined mechanisms for Class Ib and Class IV antiarrhythmic drugs (Hauswirth & Singh, 1979) against supraventricular and ventricular arrhythmias under various pathological conditions. Nevertheless, in clinical practice, care should be taken to avoid its undesirable side effects including depressant effects on cardiac automaticity, conductivity and contractility as well as a possible arrhythmogenic action at toxic doses.

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