Electrophysiological action of bepridil on atrioventricular accessory pathways

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SUMMARY The electrophysiologic properties of bepridil, a calcium channel blocker with additional effects on fast response tissues, were investigated in 10 patients with atrioventricular accessory pathways. Seven patients had Wolff-Parkinson-White syndrome, and three had concealed atrioventricular pre-excitation. A dose of 4mg/kg was administered intravenously over five minutes. Bepridil increased the AH interval and the functional refractory period of the atrioventricular node. The effective refractory periods of the right atrium and right ventricle were also increased. Bepridil prolonged refractoriness in the accessory pathway both in the anterograde and retrograde direction. After bepridil administration it was impossible to induce reciprocating tachycardia electrically in two patients because of conduction block in the normal pathway. On the other hand, the zone of tachycardia was often increased after bepridil. Nevertheless, the heart rate during tachycardia was slowed by depression of conduction in both the normal and accessory pathways.

The findings of this study provide a basis for the antiarrhythmic action of bepridil in patients with atrioventricular accessory pathways.

Bepridil, which was initially developed as an antianginal drug,1-3 has been shown to have electrophysiological effects on the heart. As a calcium antagonist the compound depresses slow responses in the sinus node and the atrioventricular node.4 In vitro studies, however, have also shown that bepridil has class I antiarrhythmic activity and reduces the maximum rate of depolarisation in fast response tissues (myocardium, Purkinje fibres).5 These findings are consistent with the widespread electrophysiological changes induced in the human heart by bepridil.6-10 Preliminary reports have underlined the value of bepridil in the treatment of cardiac arrhythmias.11-16 The present study was performed to evaluate the effects of bepridil on the Wolff-Parkinson-White syndrome and the associated reentry tachycardias.

Patients and methods

We studied 10 patients (six men and four women) aged 14 to 55 years (mean 33). Seven had Wolff-Parkinson-White syndrome (type A in four and type B in three) and three had concealed pre-excitation with accessory pathways conducting only in the retrograde direction. Spontaneous episodes of tachycardia were found in nine patients (paroxysmal supraventricular tachycardia in seven and atrial fibrillation in two). There was no evidence of other heart disease in any of these patients. After informed consent, electrophysiological studies were performed on patients in the post-absorptive, non-sedated state. Cardioactive drugs were discontinued at least seven days before the study. None of the patients was receiving amiodarone.

We used the Seldinger technique to introduce four electrode catheters via the right and left femoral veins. Two were positioned in the right atrium, one to pace the upper septal region and the other to record a bipolar electrogram from the external wall. His bundle potential was measured with a tripolar
catheter electrode. The fourth catheter electrode was used to pace the right ventricular apex. In addition, a quadripolar catheter electrode was inserted via the left basilar vein and positioned in the coronary sinus to record left atrial activity. The proximal terminals of the His bundle catheter were connected to an electrocardiogram amplifier. Intracardiac electrograms were filtered between 50 and 700 Hz. We used an eight channel direct ink-jet recorder (Elema, Sweden) with paper speeds of 100 or 200 mm/s. Five external leads (I, II, III, V1, V6) were recorded simultaneously. Cardiac pacing was done by means of a programmable modular stimulator (Janssen, Belgium). Electrical impulses (1.5 ms) were delivered at twice diastolic threshold intensity. All data recorded throughout the study were stored on magnetic tape (Hewlett-Packard).

Electrical stimulation was applied successively to the atria and ventricles. Pacing at increasing rates was used to assess the functional properties of the conduction pathways. Cardiac refractory periods were determined by the extrastimulus method. During regular pacing of the heart, increasingly premature depolarisations were elicited every eighth complex (the coupling interval was reduced by 10 ms steps) until any response disappeared.

Electrically induced reciprocating tachycardias were analysed. The mode of onset and termination, cycle length, and conduction data were taken into account. Repeat studies were performed 10 minutes after intravenous administration of bepridil (4 mg/kg over five minutes). Blood samples were collected 10, 20, and 30 minutes after injection to measure plasma concentrations of bepridil. The results were analysed statistically by the Student t test for paired data.

**Results**

Table 1 shows the effects of bepridil on atrioventricular node-His conduction. The AH interval was determined before and after bepridil administration in nine patients. After bepridil the atrioventricular nodal conduction time was increased in seven patients, reduced in one patient, and unaltered in another. There was an insignificant mean increase of 8 ms in the AH interval. The effect on the HV interval was assessed in the three patients with concealed pre-excitation. The HV interval was increased in two patients by five and 10 ms respectively and unchanged in the third patient.

The effective refractory period of the atrioventricular node could not be measured accurately both before and after the drug in any of the patients. In four patients bepridil had measurable effects on the functional refractory period of the atrioventricular node. The refractoriness of the atrioventricular node was lengthened in three patients and unchanged in the fourth. The mean increase of 55 ms was not statistically significant. The effective refractory period of the right atrium was increased in nine patients and was unaltered in one patient. The mean increase was 26 ms (p < 0.005). The effective refractory period of the right ventricle was increased in eight patients and unchanged in two patients. The mean increase was 18 ms (p < 0.005).

Table 2 shows the changes in the accessory pathways. The effective refractory period in the anterograde direction, which was measured before and after bepridil administration in four patients, was increased in all four by an average of 45 ms (p < 0.02). In another patient, all pre-excitation was abolished after bepridil administration. The
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effective refractory period in the retrograde direction was increased in one patient by 60 ms and in another by 50 ms. The shortest cycle associated with 1:1 atrioventricular conduction by the abnormal pathway during rapid atrial pacing was measured in six patients with overt pre-excitation. After bepridil the cycle length was increased by an average of 40 ms (p < 0.005).

During ventricular stimulation at increasing frequency, the shortest cycle length permitting 1:1 retrograde conduction by the abnormal pathway could be measured in eight patients before and after bepridil administration and increased in all patients (mean 43 ms, p < 0.001).

In eight patients, reciprocating tachycardia could be induced by a single premature stimulus delivered during regular cardiac pacing (table 3). One patient only developed episodes of tachycardia in response to premature atrial or ventricular depolarisations provoked in sinus rhythm. In the remaining patient, induction of tachycardia required two ventricular extrastimuli delivered during pacing of the right ventricle. The zone of tachycardia was measured only in cases in which tachycardia was produced by a single extrastimulus elicited during regular pacing.

In four patients a zone of tachycardia could be demonstrated by premature atrial stimulation before and after bepridil administration (table 3). The zone width increased in all four cases after bepridil (mean increase 60 ms). Two other patients showed a zone of tachycardia only after bepridil. On the other hand, in two other patients no sustained tachycardia was inducible by premature atrial stimulation after bepridil administration: only atrial echoes persisted, which in one patient were accompanied by non-propagated His bundle depolarisations. In five patients, a zone of tachycardia was obtained by premature ventricular stimulation before and after bepridil administration. After bepridil the zone width was increased in four of these patients by an average of 67 ms and unchanged in the fifth patient. In two other patients, the zone of tachycardia appeared after bepridil administration.

Tachycardia was recorded before and after

| Table 2 Effect of bepridil on accessory pathways (all values are ms) |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Case No | Ante ERP AP | Retro ERP AP | 1:1 ante min PCL | 1:1 retro min PCL |
| PCL | C | B | C | B | C | B | C | B |
| 1 | 500 | <220 | <260 | 500 | <220 | <230 | 225 | 250 | 275 | 300 |
| 2 | 500 | 280 | 320 | 500 | <190 | <220 | 250 | 300 | 275 | 350 |
| 3 | 500 | 310 | 270 | 500 | 300 | 360 | 275 | 300 | 275 | 300 |
| 4 | 500 | 250 | 270 | 500 | 270 | 320 | 275 | 300 | <300 | 300 |
| 5 | 500 | <240 | <260 | 500 | 270 | <260 | 225 | 300 | 250 | 325 |
| 6 | 500 | 220 | 270 | 350 | <185 | <200 | 200 | 240 | 200 | 250 |
| 7 | 500 | <220 | <270 | 400 | <220 | 270 | 225 | 250 | 225 | <275 |
| Mean (1 SD) | 242 (29) | 287 (24) | 285 (21) | 340 (28) | 233 (26) | 273 (29) | 241 (33) | 284 (42) |
| p value | <0.02 | 0.05 | 0.01 | 0.005 | 0.005 | 0.001 |

Ante, anterograde; retro, retrograde; min PCL, minimum pacing cycle length. See footnote to table 1 for other abbreviations.
bepridil administration in eight patients. In all cases the cycle length increased (mean 54 ms, p < 0.005) (table 3). The AH interval was increased in seven patients and reduced in one patient (mean increase 26 ms; NS). The HV interval was altered in only two patients (increased by 5 and 10 ms). The VA interval, related to retrograde conduction via the accessory pathway, showed an increase in five patients and no change in three others (mean increase 27 ms; NS).

Bepridil was well tolerated in all patients. The mean (1 SD) plasma concentration of the drug was 1.20 (0.39) mg/l.

**Discussion**

Previous clinical studies have shown that intravenous bepridil, in addition to reducing the sinus rate, prolongs the AH interval and the effective refractory period of the atrioventricular node. Changes consistent with blockade of the slow calcium channel. Furthermore, bepridil can depress intraventricular conduction and usually increases atrial and ventricular refractory periods. Because bepridil also has this effect on fast response tissues it would be expected to produce electrical changes in the atrioventricular accessory pathways. The results of our study confirmed this prediction. Bepridil increased the refractoriness of the accessory pathways during both anterograde and retrograde conduction as was shown by the extrastimulus method and rapid cardiac pacing. Rowland et al recorded the clinical electrophysiological effects of bepridil (2 mg/kg intravenously) in 20 patients with atrioventricular reentrant tachycardia, but they did not examine its effects on the accessory atrioventricular pathways. When Roy et al used intravenous bepridil (4 mg/kg) in four patients they found only an increase in the retrograde effective refractory period of the accessory pathway.

The dual atrioventricular conduction pathways in patients with manifest concealed pre-excitation accounts for the development of circus movement tachycardias. In the most common variety the reentrant impulse is conducted in an anterograde fashion through the atrioventricular node and the bundle of His and returns to the atria via the accessory pathway. The antiarrhythmic activity of a drug may affect the factors initiating reentry—that is, extrasystoles and/or the circuit itself in which the wave of tachycardia progresses. The reported suppression of ventricular extrasystoles by bepridil may therefore be beneficial in patients with accessory pathways. The depressant effect of bepridil on all parts of the atrioventricular reentry circuit should be useful in controlling reciprocating tachycardias. After bepridil two of the 10 patients in the present study no longer had electrically inducible tachycardia because they had conduction blocks within the atrioventricular node and the His-Purkinje system respectively. Often, however, there was an increase in the reentry zone. This paradoxical effect has also been seen with other drugs. Antiarrhythmic action requires a critical balance between the changes in conduction velocity and the effective refractory period within the circuit. Without such a balance, qualitatively similar effects may favour the development of circus movement thus in this series bepridil caused electrophysiological
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Changes that were clearly arrhythmogenic. Such responses to the drug have not been described previously. The clinical implications are unknown. Tachycardia during bepridil administration had a longer cycle length, an effect related to the depression of conduction in both the normal and accessory pathway. The role of bepridil in the treatment of supraventricular tachycardias remains unclear. Rowland et al reported that intravenous bepridil terminated reentry tachycardias associated with atrioventricular accessory pathways in half the cases. The basis of this action was the development of an antegrade block in the atrioventricular node. There are no available data on the short term prevention of recurrences.

The results of the present study also indicate that bepridil may be useful in the treatment of atrial tachycardia of the Wolff-Parkinson-White syndrome. In this case, conduction via the accessory pathway is a possible source of life threatening high ventricular rates. By increasing the antegrade effective refractory period of the accessory connection, bepridil may well slow down the ventricular response during atrial fibrillation. This is supported by recent findings on electrically induced episodes of atrial fibrillation. In contrast, verapamil accelerated the ventricular response. Furthermore, the prolongation of the atrial refractory period may have a role in the short term control of atrial arrhythmias.

Roy et al reported comparable electrophysiological effects on atrioventricular accessory pathways after oral bepridil. The plasma concentration of the drug was not measured. The doses used (300–400 mg/day), however, give mean blood concentrations of 1–2 mg/l—that is in the range of the present study. Supraventricular tachycardia was prevented in five of the 11 patients on oral bepridil. Moreover, the results of repeat testing during oral treatment predicted the clinical outcome. Because ours was not a long term study we cannot draw definite conclusions about the predictive value of acute testing with intravenous bepridil.

The role of bepridil in patients with atrioventricular accessory pathways deserves further investigation. Additional information on the safety margin is required because several cases of torsade de pointes have been reported during bepridil treatment. Studies now in progress in France aim at providing a precise answer to this question.

References

Touboul, Atallah, Kirkorian, Lavaud, Kiency, Mathieu, Dellinger