Pharmacology of Bepridil

Alan Gill, PhD, Stephen F. Flaim, PhD, Bruce P. Damiano, PhD, Siu Po Sit, PhD, and Melvin D. Brannan, PhD

Bepridil is an antianginal agent with multiple therapeutic actions. It decreases calcium influx through potential-dependent and receptor-operated sarcolemmic calcium channels and acts intracellularly as a calmodulin antagonist and calcium sensitizer. Thus, in cardiac muscle it enhances the sensitivity of troponin C to calcium, stimulates myofibrillar adenosine triphosphatase activity, removes calmodulin's inhibitory effect on sarcoplasmic reticulum calcium release, and inhibits sodium–calcium exchange—actions that tend to offset the effects of calcium influx blockade on cardiac contractile force. However, in vascular smooth muscle where the calcium–calmodulin complex promotes muscle contraction by activating myosin light-chain kinase phosphorylation of contractile proteins, calmodulin antagonism, coupled with bepridil's blockade of calcium influx, leads to vasorelaxation. In animal models of ischemia, bepridil and other calmodulin inhibitors show antiarrhythmic efficacy following reperfusion. Additionally, interfering with calmodulin's role in sympathetic nerve terminal function may help to limit the ischemia-induced catecholamine release that contributes to arrhythmogenesis. Bepridil shows a lidocaine-like fast kinetic block of inward sodium current (as distinct from the slow or intermediate kinetic inhibition expressed by encainide or quinidine, respectively). This inhibition is pH-dependent; activity is expressed to a greater degree at lower pH levels. Thus, this potentially antiarrhythmic mechanism is activated by conditions of ischemia. Bepridil's blockade of outward potassium currents and its inhibition of sodium–calcium exchange increase action potential duration and ventricular refractoriness, prolong the QT interval, and form the basis for a class III antiarrhythmic mechanism. Because hypokalemia also prolongs the QT interval, the addition of bepridil in the presence of hypokalemia can lead to excessive prolongation. Bepridil both increases myocardial oxygen supply through coronary vasodilation and decreases myocardial oxygen demand through mild heart rate and afterload reduction, and shows potential antiarrhythmic activity through class IB, III, and IV mechanisms. In addition, its ability to inhibit receptor-operated calcium influx, a property that distinguishes it from other calcium antagonists, could have additional therapeutic benefits against ischemia and atherosclerosis.

(Am J Cardiol 1992;69:11D–16D)

Bepridil is a new, long-acting antianginal agent with multiple therapeutic actions that combine to increase myocardial oxygen supply and to reduce myocardial oxygen demand. Part of bepridil's therapeutic efficacy can be attributed to its inhibition of calcium influx through voltage-dependent channels. However, it has a number of other actions, both at the cell membrane and at the intracellular level, that distinguish it from other calcium antagonists. These actions help to minimize any negative impact on cardiac contractility and systemic blood pressure, and to increase its antianginal efficacy compared with currently available calcium antagonists. These actions also impart unique electrophysiologic properties that have potential antiarrhythmic utility.

CELL MEMBRANE EVENTS

Several of bepridil's mechanisms of action at the cell membrane level affect cardiac electrophysiology.

Slow calcium channel inhibition: Among bepridil's sarcolemmic actions, its slow calcium channel inhibition[1,2] can influence sinoatrial (SA) and atrioventricular (AV) nodal function. Generally, calcium influx blockade tends to decrease SA nodal automaticity and decrease heart rate, as well as delay AV nodal conduction and prolong PR interval.[3,4] However, the magnitude of these effects varies among calcium channel inhibitors because it

From the Department of Cardiovascular Pharmacology, R.W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania.

Address for reprints: Alan Gill, PhD, McNeil Pharmaceutical R-355, McKean and Welsh Roads, Spring House, Pennsylvania 19477.

is markedly influenced by tissue selectivity and the degree to which compensatory autonomic-reflex responses are elicited by the respective calcium channel inhibitor. Bepridil produces little reduction in systemic blood pressure to elicit compensatory reflexes; mild heart-rate reduction and prolongation of AV nodal conduction time are expressed in vivo.[5–7]

Fast sodium channel inhibition: Bepridil also inhibits cardiac fast sodium channels in a manner similar to lidocaine.[2,8–10] This inhibition is pH-dependent and is expressed to a greater degree at lower pH levels.[11] Thus, this potentially antiarrhythmic mechanism is activated by conditions of ischemia.

Although slow kinetic sodium channel inhibitors (e.g., flecainide, encainide, transcainide) have proved to be unacceptably arrhythmogenic, lidocaine, a fast kinetic sodium channel inhibitor, has proven very safe. Bepridil inhibits sodium channels in a manner similar to lidocaine.[9,12,13]

Sodium–calcium exchange inhibition: Inhibiting sodium–calcium exchange may contribute to QT prolongation produced by bepridil; amiloride behaves similarly. During phases of the action potential when membrane potential is depolarized (depolarization, plateau, and initial part of repolarization), sodium–calcium exchange is directed to push out sodium and take in calcium. During the longer, more polarized phases of the action potential (late repolarization and rest), the exchanger takes in sodium and pushes out calcium, reducing intracellular calcium levels. Its action during plateau and early repolarization tends to shorten the action potential duration. Bepridil's inhibition of the exchanger[14,15] tends to prolong the action potential duration.

Inhibition of outward repolarizing potassium currents: Class III antiarrhythmic drugs also prolong the action potential duration, but do so primarily by inhibiting potassium-repolarizing currents. In addition to its effects on the sodium–calcium exchanger, bepridil also shows the ability to inhibit repolarizing potassium currents[16] and behaves like a class III antiarrhythmic agent to increase ventricular refractoriness through prolongation of the action-potential duration.[1,9,10,13,17]

Bepridil's cell membrane actions influence cardiac conduction in a manner different from other calcium antagonists (Figure 1). In addition to affecting cardiac muscle function, bepridil also affects vascular smooth muscle cell membrane function.

Inhibition of potential-dependent and receptor-operated calcium channels in vascular smooth muscle: Calcium antagonists, as a class, are able to inhibit calcium influx through potential-dependent calcium channels, thereby decreasing available calcium for contraction in both cardiac and vascular smooth muscle. Bepridil shares this property with other calcium antagonists. However, unlike other calcium antagonists, bepridil also inhibits calcium influx through receptor-operated calcium channels[18] (Figure 2).

Whereas opening of potential-dependent calcium channels is activated through a membrane voltage sensor, opening of receptor-operated calcium channels is activated through binding of a specific agonist to its membrane receptor. Receptor activation is associated with calcium influx

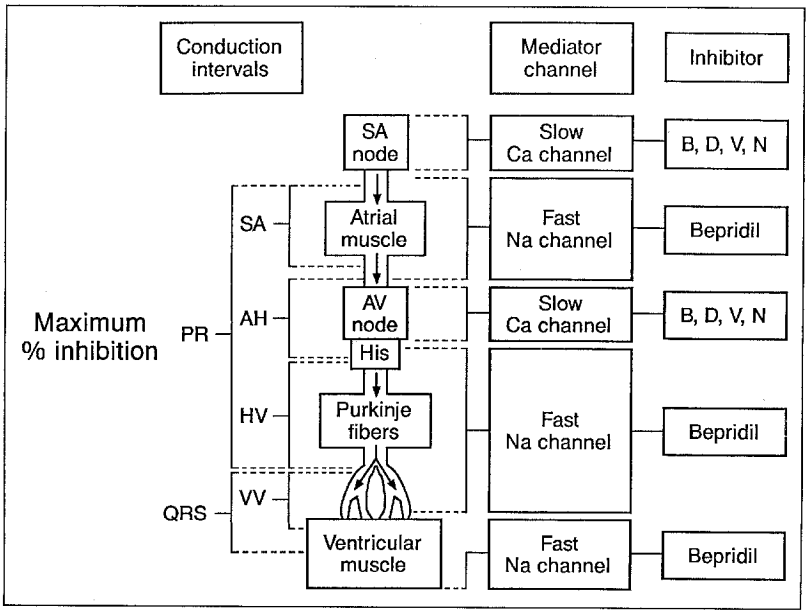

FIGURE 1. Effects of calcium antagonists on cardiac excitation and conduction. AH = atrioventricular nodal conduction interval; B = bepridil; Ca = calcium; D = diltiazem; HV = His–Purkinje conduction interval; N = nifedipine; Na = sodium; SA = sinoatrial conduction interval; V = verapamil; VV = ventricular conduction interval.

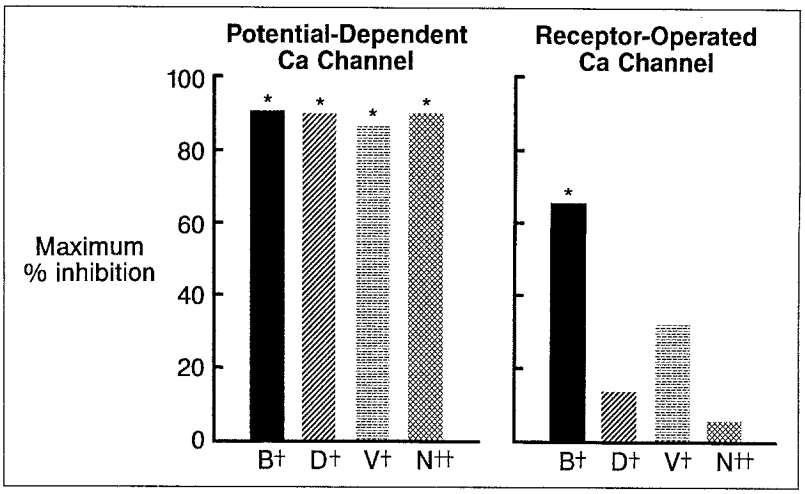

FIGURE 2. Contractile activity of calcium antagonists in rabbit aorta. B = bepridil; D = diltiazem; N = nifedipine; V = verapamil. *p <0.05; †100 μM (n = 6); ††10μM (n = 6).

through the receptor-coupled channel and also with the stimulation of phosphatidylinositol turnover. The inositol triphosphate and diacylglycerol signals thus produced activate intracellular processes that promote contractility.

For agonists such as norepinephrine ($\alpha_1$adrenoceptors), serotonin (5-HT_2), and angiotensin II, sustained receptor activation has been associated not only with contraction, but also with vascular smooth-muscle proliferation. Thus, sustained agonism by these mediators stimulates growth-factor production, which can contribute to the process of atherogenesis. Conversely, interrupting the function of these mediators by any method can prevent atherogenesis in animal models of atherosclerosis. Whether bepridil's inhibition of receptor-operated calcium channels can inhibit the process of atherogenesis remains to be seen. Interestingly, the low density lipoprotein (LDL) receptor is also coupled to a receptor-operated calcium channel.

INTRACELLULAR EVENTS

Whereas nifedipine and diltiazem do not achieve significant intracellular levels (Figure 3), bepridil penetrates the cell membrane and has important intracellular actions. Although intracellular verapamil levels seem significant in Figure 3, these levels appear to result from verapamil binding to the intracellular surface of the cell membrane and to be associated with actions at the level of the cell membrane, rather than with intracellular actions of verapamil.[19]

In addition to direct action, it is possible to modify intracellular calcium levels indirectly. For example, calmodulin is a ubiquitous eukaryotic protein that binds calcium, and this calcium-protein complex then interacts in the regulation of many basic cellular functions. Bepridil has been shown to *inhibit* intracellular calmodulin-dependent processes, thereby acting as a calmodulin antagonist. Thus, in vascular smooth muscle where the calcium–calmodulin complex promotes muscle contraction by activating myosin light-chain kinase phosphorylation of contractile proteins, bepridil's calmodulin antagonism (Figure 4), together with its calcium influx blockade, leads to vasorelaxation.[20–24]

In cardiac muscle, however, bepridil's calmodulin inhibition *promotes* calcium availability by removing the inhibitory effect of calmodulin on sarcoplasmic reticulum calcium release. This action, along with bepridil's ability to sensitize cardiac troponin C to calcium and to stimulate myofibrillar adenosine triphosphatase activity (Figure 5), tends to offset the effects of calcium influx blockade on cardiac contractile force.[25,26] These intracellular effects in cardiac muscle are theorized to account for bepridil's lesser negative inotropic effect and

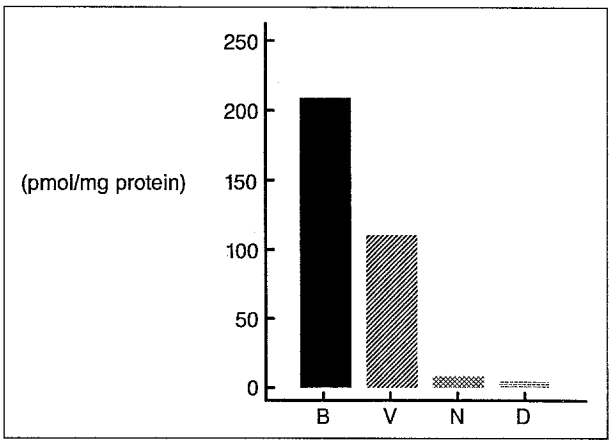

FIGURE 3. Uptake of drug into cardiac muscle cells. B = bepridil; D = diltiazem; N = nifedipine; V = verapamil. (Reprinted with permission from *Eur J Pharmacol*.[19])

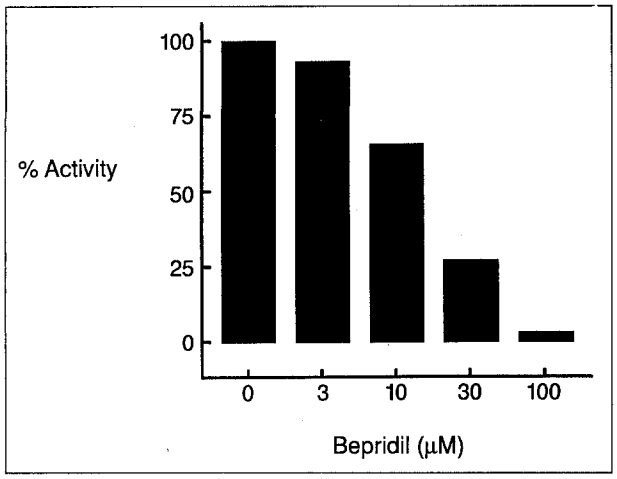

FIGURE 4. Effect of bepridil on calcium–calmodulin-induced myosin light chain kinase activity. (Reprinted with permission from *J Pharmacol Exp Ther.*[20])

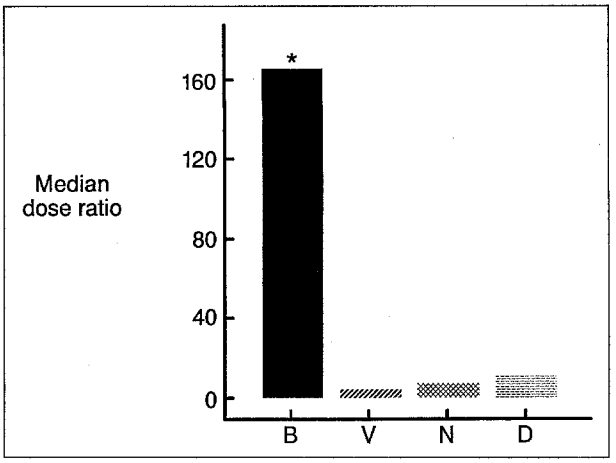

FIGURE 6. Negative inotropic/coronary dilator dose ratios in guinea pig Langendorff heart. B = bepridil; D = diltiazem; N = nifedipine; V = verapamil. *p <0.05 compared with other agents.

may distinguish it from other calcium antagonists (Figure 6).[27]

Calmodulin inhibition also may contribute to bepridil's antiarrhythmic activity. Bepridil and other calmodulin inhibitors show antiarrhythmic efficacy in animal models of ischemia followed by reperfusion.[28–32] Additionally, interfering with calmodulin's role in sympathetic nerve terminal function may help to limit ischemia-induced catecholamine release, which contributes to arrhythmogenesis.[33]

SYSTEMIC PHARMACOLOGY

Bepridil's intracellular and cell membrane level actions combine to produce systemic effects that have potential antianginal and antiarrhythmic efficacy. In animal models, bepridil consistently causes a small but significant heart-rate reduction, which can contribute to reducing myocardial oxygen consumption.[34] As shown in Figure 7, bepridil both increases myocardial oxygen supply through coronary vasodilation and decreases myocardial oxygen consumption. The reduction in myocardial oxygen consumption does not appear to be achieved through reduction in cardiac contractility (Figure 8).[35] Bepridil's effects on action-potential duration lead to a significant increase in the ventricular effective refractory period (Figure 9). This effect can slow or abolish abnormal automaticity within the infarct zone and terminate reentrant arrhythmias in animal models of ischemic arrhythmogenesis.[17]

CONCLUSION

Bepridil is a new antianginal agent with an intrinsically long duration of action (mean elimination half-life, 42 hours).[36] It shares some properties with conventional calcium antagonists such as nifedipine, verapamil, and diltiazem. Thus, bepridil can inhibit calcium influx through potential-dependent calcium channels in cardiac and vascular smooth muscle and slow AV nodal conduction. However, a number of additional actions distinguish bepridil from conventional calcium antagonists.

Through its blockade of outward-repolarizing

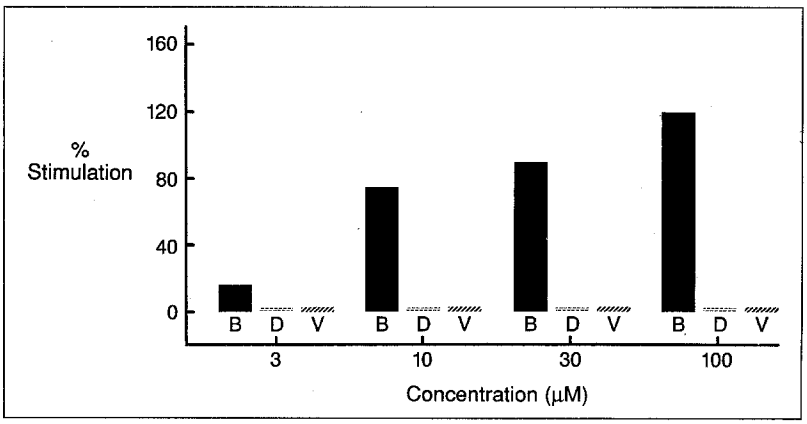

FIGURE 5. Effect of bepridil (B), diltiazem (D), and verapamil (V) on cardiac myofibrillar adenosine triphosphatase activity. (Reprinted with permission from *J Pharmacol Exp Ther.*[26])

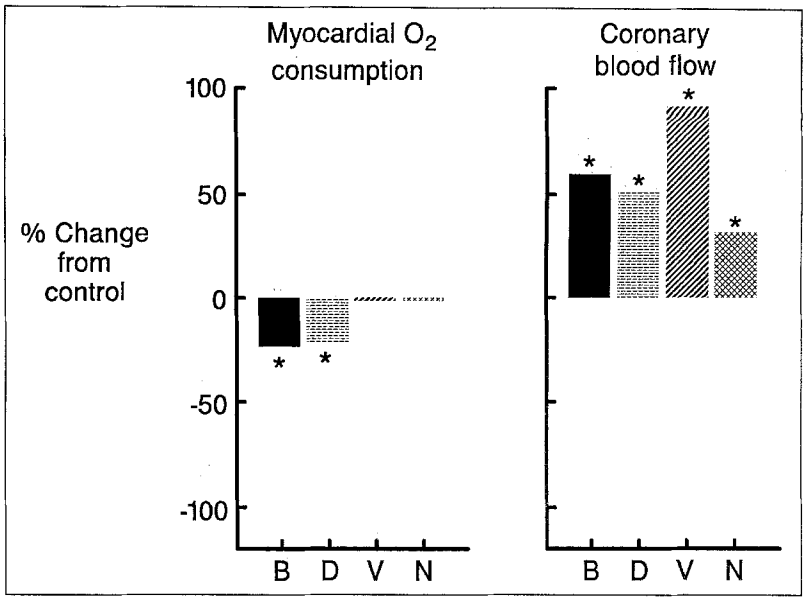

FIGURE 7. Effects of calcium antagonists on myocardial oxygen consumption and coronary blood flow in anesthetized dog. B = bepridil (4.0 mg/kg); D = diltiazem (0.2 mg/kg); N = nifedipine (0.004 mg/kg); V = verapamil (0.015 mg/kg). *p <0.05.

potassium currents and inhibition of sodium–calcium exchange, bepridil prolongs action potential duration and QT interval and increases ventricular refractoriness. This action supports bepridil's class III antiarrhythmic activity and carries with it the necessity of guarding against excessive QT prolongation.

In addition to inhibiting calcium influx through potential-dependent channels, bepridil also inhibits influx through receptor-operated calcium channels associated with vasoconstrictor and growth factor functions of important vasoactive agonists. The implications of this action are not understood fully. However, it has the potential to inhibit both vasospastic and vascular proliferative factors important in angina pectoris as well as underlying coronary atherosclerosis.

Unlike conventional calcium antagonists, bepridil can act as a calmodulin inhibitor. This property

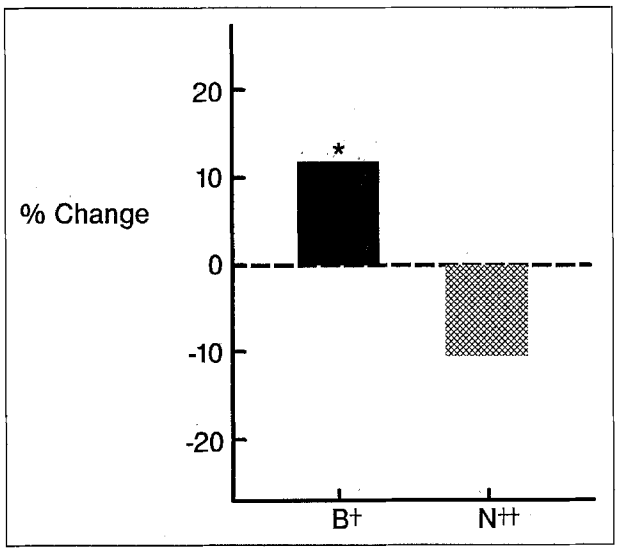

FIGURE 8. Effect of bepridil (B) and nifedipine (N) on cardiac contractility (*dP/dt*) in conscious rat. *p <0.005 compared with parallel vehicle; †21.0 mg/kg intravenously; ††0.6 mg/kg intravenously.

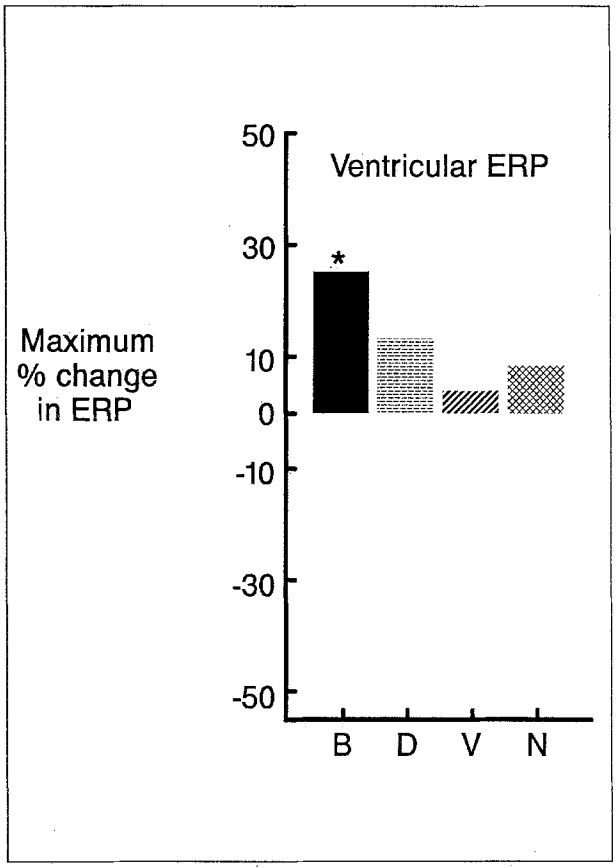

FIGURE 9. Effects of calcium antagonists on ventricular effective refractory period (ERP) in anesthetized dog. B = bepridil (2.5 mg/kg intravenously; D = diltiazem (0.3 mg/kg intravenously); N = nifedipine (0.17 mg/kg intravenously); V = verapamil (0.3 mg/kg intravenously). *p <0.05.

decreases contractility in vascular smooth muscle, where calmodulin promotes the phosphorylation of contractile proteins that results in amplification of contractility. On the other hand, inhibition of calmodulin in cardiac muscle increases calcium availability for contraction. When combined with bepridil's ability to stimulate calcium–troponin binding and its ability to stimulate myosin adenosine triphosphatase activity, these actions tend to offset the effects of calcium-entry blockade in cardiac muscle and may account for bepridil's lesser negative inotropic effect compared with conventional calcium antagonists.

Bepridil shows a rapid kinetic, pH-dependent, lidocaine-like inhibition of sodium current, which can result in slowed atrial and ventricular conduction. Although this slowing does not result in QRS widening at normal therapeutic doses, it can become more prominent under ischemic conditions because of its pH dependence. Consequently, this contributes class IB antiarrhythmic properties to bepridil's actions.

The net effect of bepridil's multiple actions is to increase myocardial oxygen supply and decrease myocardial oxygen consumption, ideal properties of an antianginal agent. It does so with little reduction in systemic blood pressure and with lesser negative inotropic potential than traditional calcium antagonists. This mode of action, coupled with the convenience of once-daily dosing, provides bepridil with a pharmacologic profile well suited to use in patients with refractory angina pectoris.

REFERENCES

1. Vogel S, Crampton R, Sperelakis N. Blockade of myocardial channels by bepridil (CERM-1978). *J Pharmacol Exp Ther* 1979;210:378–385.

2. Yatani A, Brown AM, Schwartz A. Bepridil block of cardiac calcium and sodium channels. *J Pharmacol Exp Ther* 1986;237:9–17.

3. Goto J, Sperelakis N. Depression of automaticity of the rabbit SA node by bepridil and nifedipine. *Eur J Pharmacol* 1984;99:227–231.

4. Damiano BP, Ludovici KA, Brannan MD. Effects of bepridil hydrochloride on cardiac conduction in anesthetized dogs. McNeil Pharmaceutical Biological Research Report, BRR No. 089–00(860407), Spring House, PA, 1986.

5. Singh BN, Nademanee K, Feld G, Pointek M, Schwab M. Comparative electrophysiologic profiles of calcium antagonists with particular reference to bepridil. *Am J Cardiol* 1985;55(suppl):14C–19C.

6. Rowland E, McKenna WJ, Krikler DM. Electrophysiologic and antiarrhythmic actions of bepridil. *Am J Cardiol* 1985;55:1513–1519.

7. Prystowsky EN. Electrophysiologic and antiarrhythmic properties of bepridil. *Am J Cardiol* 1985;55(suppl):59C–62C.

8. Lathrop DA, Murphy AM, Humphreys T, Schwartz A. Effects of bepridil on force development and transmembrane electrical activity of adult canine Purkinje strands: comparison with nisoldipine and lidocaine. *Eur J Pharmacol* 1985;118:283–292.

9. Anno T, Furuta T, Itoh M, Kodama I, Toyama J, Yamada K. Effects of bepridil on the electrophysiological properties of guinea-pig ventricular muscles. *Br J Pharmacol* 1984;81:589–597.

10. Winslow E, Kane A. Supraventricular antidysrhythmic and electrophysiological effects of bepridil, a new antianginal agent. *J Cardiovasc Pharmacol* 1981;3:655–667.

11. Shank RP, Bryan DJ. Evaluation of bepridil hydrochloride as a sodium channel blocker in rat brain synaptosomes. McNeil Pharmaceutical Biological Research Report, BRR No. 190–00(880928), Spring House, PA, 1988.

12. Dietrich H, Borchard U, Hafner D, Hirth C. Antiarrhythmic and electrophysiological actions of flecainide, bepridil and amiodarone on isolated heart preparations during controlled hypoxia. *Arch Int Pharmacodyn Ther* 1985;274:267–282.

13. Kane KA, Berdeja-Garcia GY, Sanchez-Perez S, Pastelin G. Electrophysiological effects of lidocaine, 1-chlorpheniramine, and bepridil on rabbit sinus node pacemaker cells. *J Cardiovasc Pharmacol* 1983;5:102–108.

14. Kaczorowski GJ, Slaughter RS, Garcia ML, King VF. Block of cardiac sodium-calcium exchange by mechanism-based inhibitors. *Progr Clin Biol Res* 1988;252:261–266.

15. Van Amsterdam F Th M, Zaagsma J. pH-Dependent effects of bepridil on Ca^{2+}-extrusion across rat heart sarcolemma. *Arch Int Pharmacodyn Ther* 1989;298:90–95.

16. Berger F, Borchard U, Hafner D. Effects of the calcium entry blocker bepridil on repolarizing and pacemaker currents in sheep cardiac Purkinje fibres. *Naunyn Schmiedeberg's Arch Pharmacol* 1989;339:638–646.

17. Dangman KH. Effects of bepridil on transmembrane action potentials recorded from isolated canine cardiac tissues. *Naunyn Schmiedeberg's Arch Pharmacol* 1985;329:326–332.

18. Flaim SF, Ratz PH, Swigart SC, Gleason MM. Bepridil hydrochloride alters potential-dependent and receptor-operated calcium channels in vascular smooth muscle of rabbit aorta. *J Pharmacol Exp Ther* 1985;234(1):63–71.

19. Pang DC, Sperelakis N. Nifedipine, diltiazem, bepridil and verapamil uptake into cardiac and smooth muscles. *Eur J Pharmacol* 1983;87:199–207.

20. Itoh H, Ishikawa T, Hidaka H. Effects on calmodulin of bepridil, an antianginal agent. *J Pharmacol Exp Ther* 1984;230:737–741.

21. Itoh H, Tanaka T, Mitani Y, Hidaka H. The binding of the calcium channel blocker bepridil, to calmodulin. *Biochem Pharmacol* 1986;35:217–220.

22. Lugnier C, Follenius A, Gerard D, Stoclet JC. Bepridil and flunarizine as calmodulin inhibitors. *Eur J Pharmacol* 1984;98:157–158.

23. Barron E, Marshall RJ, Martorana M, Winslow E. Comparative antiarrhythmic and electrophysiological effects of drugs known to inhibit calmodulin (TFP, W7 and bepridil). *Br J Pharmacol* 1986;89:603–612.

24. Agre P, Virshup D, Bennett V. Bepridil and cetiedil, vasodilators which inhibit Ca^{++}-dependent calmodulin interactions with erythrocyte membranes. *J Clin Invest* 1984;74:812–820.

25. El-Saleh SC, Solaro RJ. Calmidazolium, a calmodulin antagonist, stimulates calcium-troponin C and calcium-calmodulin-dependent activation of striated muscle myofilaments. *J Biol Chem* 1987;262:17240–17246.

26. Solaro RJ, Bousquet P, Johnson JD. Stimulation of cardiac myofilament force, ATPase activity and troponin C Ca^{++} binding by bepridil. *J Pharmacol Exp Ther* 1986;238:502–507.

27. Massingham R, Van Zwieten PA. Bepridil: a pharmacological reappraisal of its potential beneficial effects in angina and tissue protection following ischemia. *Cardiovasc Drugs Ther* 1989;3:731–742.

28. Chollet-Debord F, Moins N, Gachon P, Duchene-Marullaz P. Comparison of verapamil and bepridil, two slow channel inhibitors, in protection against calcium-induced arrhythmias. *Naunyn Schmiedeberg's Arch Pharmacol* 1986;334:105–109.

29. Marshall RJ, Muir AW. The beneficial actions of bepridil in acute myocardial infarction in anesthetized dogs. *Br J Pharmacol* 1981;73:471–479.

30. Lynch JJ, Montgomery DG, Ventura A, Lucchesi BR. Antiarrhythmic and electrophysiologic effects of bepridil in chronically infarcted conscious dogs. *J Pharmacol Exp Ther* 1985;234:72–80.

31. Leboeuf J, Leoty C, Lamar JC, Massingham R. Comparative effects of bepridil, its quaternary derivative CERM 11888 and verapamil on caffeine-induced contracture in ferret hearts. *Br J Pharmacol* 1989;98:119–126.

32. Leboeuf J, Lamar JC, Massingham R, Ponsonnaille J. Electrophysiological effects of bepridil and its quaternary derivative CERM 11888 in closed chest anesthetized dogs: a comparison with verapamil and diltiazem. *Br J Pharmacol* 1989;98:1351–1359.

33. Guo Z-G, Tang X-L. Norepinephrine release during ischemia/reperfusion and the effects of bepridil and propranolol on myocardial injury in isolated working guinea pig hearts. *Eur J Pharmacol* 1990;183:603–604.

34. Beaughard M, Ferrier M, Labrid JC, Leboeuf J, Piris P. Studies on the bradycardia induced by bepridil. *Br J Pharmacol* 1982;75:293–300.

35. Flaim SF, Stranieri MT, Mathiasen JR. Effects of bepridil hydrochloride on cardiocirculatory dynamics, coronary vascular resistance, and cardiac output distribution in normal, conscious rats. *J Cardiovasc Pharmacol* 1988;11:363–372.

36. Benet LZ. Pharmacokinetics and metabolism of bepridil. *Am J Cardiol* 1985;55(suppl):8C–13C.