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Comparative clinical efficacy of bepridil, propranolol and placebo in patients with chronic stable angina

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1 A randomised double-blind parallel group study was performed to compare the clinical efficacy of bepridil, a new calcium slow channel blocker, with that of propranolol and placebo in patients with chronic stable angina of effort.

2 Efficacy was assessed objectively by dynamic exercise testing using an upright bicycle ergometer and subjectively by patient documentation of anginal frequency and nitrate consumption.

3 The administration of bepridil resulted in a significant improvement in physical work capacity expressed as calculated maximal oxygen uptake (V_{O_2} max) and exercise time. This was associated with subjective improvement in terms of reduced anginal frequency.

4 Despite baseline differences in exercise performance and anginal frequency between the three treatment groups, the beneficial effects of bepridil were statistically significant when compared to propranolol.

5 Although minor electrocardiographic changes were noted, no adverse effects were evident when bepridil was prescribed in doses of up to 400 mg/day over a 10 week period.

Keywords bepridil propranolol angina

Introduction

At present, conventional therapy for angina pectoris consists of the use of nitrates, β-adrenoceptor blocking agents and calcium channel blockers. While most patients respond favourably to these compounds used singly or in combination (Tweddel *et al.*, 1981), these agents can depress cardiac function and up to 10% report significant adverse effects necessitating their withdrawal (Packer *et al.*, 1982; Greenblatt & Koch-Weser, 1974). The search therefore continues for new approaches to antianginal therapy.

Bepridil, 1(3 isobutoxy 2 (phenylbenzyl) amino) propyl pyrrolidine hydrochloride, is a new pharmacological agent with anti-anginal potential. This compound has been shown to depress the slow inward Ca^{++} current of the myocardium and vascular smooth muscle and is a coronary and systemic vasodilator (Vogel *et al.*, 1979; Harder & Sperelakis, 1981). In addition to inhibition of the slow inward Ca^{++} current, bepridil inhibits the fast inward Na^{+} current of the myocardium and could be classified as belonging to classes I and IV of the Vaughan-Williams classification of anti-arrhythmic drugs (Vaughan-Williams, 1970). This compound may therefore confer a dual benefit to the patient with symptomatic coronary heart disease who is prone to serious arrhythmias and sudden death. The purpose of the present study was to compare the clinical efficacy of bepridil with propranolol and place-

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bo in patients with coronary artery disease and chronic stable angina.

Methods

The study population consisted of 35 patients (33 males and two females), aged 41–69 years (mean age 54 years). The patients had coronary heart disease with chronic stable angina of at least 3 months duration. On exercise all patients experienced reproducible anterior chest discomfort associated with flat or downsloping ST segment depression of > 1 mm at 0.08 s after the J-point of the electrocardiogram. Eleven patients had historical and electrocardiographic evidence of previous myocardial infarction and 20 who had been investigated by coronary arteriography were demonstrated to have at least 70% luminal stenosis of one or more of the major epicardial vessels. Patients with recent myocardial infarction (< 3 months), systemic hypertension or significant valvular heart disease were excluded from the study. The clinical details of each patient are found in Table 1.

Approval for this study was obtained from the Ethical Committee, Glasgow Royal Infirmary, and written consent was obtained from each patient. The study protocol is shown (Figure 1). A direct group comparison was chosen rather than a crossover design as it was considered that the natural temporal variation inherent in anginal symptoms might bias results towards one study group or another. After initial assessment previously prescribed anti-anginal therapy was gradually discontinued over a 2 week period with the exception of sublingual glyceryl trinitrate which was continued throughout the study. Those patients who agreed to remain in the study and who remained symptomatic were then randomised to therapy with bepridil, propranolol or placebo in a double-blind manner. Patients were seen at 2-weekly intervals for assessment and adjustment of drug dosage. The treatment schedule is shown in the protocol, therapy being prescribed in divided dose, twice daily. Drug dosage was increased until the examining clinician considered full efficacy had been obtained or until side effects were encountered. For the purpose of the study, patients found to have a standing resting heart rate of 55 beats/min were considered to be on optimum drug dosage and the individual dose for each patient was not increased thereafter, the patient receiving this dose for the remainder of the 10-week study period.

At each visit a general clinical examination was performed and patients were questioned for possible side effects. Subjective assessment was carried out by patient diary cards documenting anginal frequency and glyceryl trinitrate consumption. Objective assessment of drug efficacy was obtained by dynamic exercise testing using a mechanically braked upright bicycle ergometer (Puch Tunturi). A symptom limited exercise test was performed using a continuous exercise protocol starting at an initial workload of 300 kilopond/metres (kpm) and rising by increments of 300 kpm at 3 min intervals until the onset of symptoms. A modified V5 lead was monitored continuously by telemetry throughout the exercise test. At the end of each exercise period and at the onset of symptoms a sample of the electrocardiogram was recorded and systemic blood pressure was measured indirectly using a conventional cuff sphygmomanometer. These parameters were also measured at intervals for 6 min into the recovery period.

Drug efficacy was judged objectively by noting the time of exercise until the onset of symptoms and the product of heart rate $\times$ systolic blood pressure was obtained as a measure of myocardial oxygen consumption (Robinson, 1967; Gobel *et al.*, 1978). Physical work capacity was assessed indirectly using a formula for maximal oxygen uptake V_{O_2} max

$$(V_{O_2}\ \text{max} = \frac{2\ (\text{total kpm}) + 300)}{\text{weight in kg}}$$

This has previously been validated as an accurate measure of physical work capacity (Blomqvist, 1973). Patient compliance was judged by tablet counts and by blood sampling for plasma drug assays. Routine biochemical and haematological parameters were measured before the administration of medication and at the end of the study period.

Statistical analysis within treatment groups was performed by paired *t*-test against baseline and intergroup analysis was carried out by analysis of covariance.

Results

Of 35 patients entering the study, 26 completed the protocol—nine on therapy with bepridil, eight on propranolol and nine receiving placebo. All patients prescribed bepridil received the maximum dose of 400 mg/day. For the propranolol group, the dose range lay between 80 mg/day and 320 mg/day with a mean propranolol dosage of 220 mg/day. In these normotensive patients with angina the mean resting heart rate was 53 beats/min.

All results refer to the mean $\pm$ s.e. mean.

Table 1 Clinical characteristics of the study population. (a) Bepridil patient group

Clinical characteristics bepridil patient group						
Sex	*Age (years)*	*Cigarettes smoked*	*Therapy*	*ECG*	*Angiography*	*Time to angina (min)*
M	59	20/day	Warfarin GTN	Widespread myocardial ischaemia +ve exercise test	—	1.3
M	53	20/day	GTN	Old inferior myocardial infarction	Inferior hypokinesia Total occlusion in RCA. 50% LAD Distal Cx occlusion	5.3
M	56	—	Propranolol	Lateral myocardial ischaemia +ve exercise test	—	4.3
M	59	—	—	Normal	Normal L.V. 78% LAD and Cx 60% RCA	1.0
M	47	20/day	GTN	Old inferior old anterior infarct	Antero-apical akinesia Inferior hypokinesia 80% RCA: LAD: Cx	5.0
M	60	—	Isosorbide	Widespread myocardial ischaemia +ve exercise test	—	2.3
M	50	40/day	Nifedipine	Normal +ve exercise test		4.0
M	58	—	GTN	Inferior myocardial ischaemia +ve exercise test	—	2.3
M	58	—	GTN	Inferior ischaemia +ve exercise test	—	4.0
M	60	—	GTN	Anterior myocardial infarction +ve exercise test	—	4.0
Mean 56 ± 2						3.2 ± 0.5

LAD = Left anterior descending artery
RCA = Right coronary artery
Cx = Circumflex coronary artery

Table 1 Clinical characteristics of the study population. (b) Placebo patient group.

Clinical characteristics placebo patient group						
Sex	*Age (years)*	*Cigarettes smoked*	*Therapy*	*ECG*	*Angiography*	*Time to angina (min)*
M	52	10/day	GTN	Old antero-septal myocardial infarct +ve exercise test	—	5.3
M	51	10/day	Nifedipine	Antero-lateral myocardial infarct	Normal L.V. Total occlusion RCA and Cx.	6.0
M	54	—	Propranolol Nifedipine	Normal	Normal L.V. 79% LAD	4.3
M	47	—	Metoprolol	Lateral ischaemia	Apical akinesia 80% RCA and LAD	2.3
M	58	10/day	GTN	Lateral ischaemia	Normal L.V. 80% RCA and LAD	4.0
M	54	—	Metoprolol	Normal	Normal L.V. 80% LAD and RCA	3.0
M	47	20/day	Propranolol	Old infer-ior myocardial infarct	Antero-apical Total occlusion RCA 80% Cx	8.0
M	59	15/day	Aprenolol Nifedipine	Normal	Normal L.V. Total occl. Cx. 89% RCA and LAD	2.0
M	50	20/day	Metoprolol	Infero-lateral myocardial ischaemia	Normal Total occlusion RCA and Cx 90% LAD	4.0
M	62	30/day	GTN	Normal +ve exercise test	—	4.0
M	60	—	GTN	Normal +ve exercise test	—	6.0
M	48	20/day	GTN	Old anterior myocardial infarct +ve exercise test	—	3.0
Mean 54 ± 2						4.5 ± 5

Table 1 Clinical characteristics of the study population. (c) Propranolol patient group.

			Clinical characteristics propranolol patient group			
Sex	*Age (years)*	*Cigarettes smoked*	*Therapy*	*ECG*	*Angiography*	*Time to angina (min)*
M	46	20/day	Nifedipine	Inferior myocardial ischaemia	Normal L.V. Total occlusion RCA 50% LAD and Cx	7.3
F	40	—	GTN	Old anterior myocardial infarct	Apical hypokinesia 80% LAD	4.0
F	57	25/day	Nifedipine	Inferior infarct	Antero-apical myocardial hypokinesia	1.3
M	47	20/day	Nifedipine	Inferior myocardial infarct	Global LV dysfunction 80% RCA: LAD: Cx.	6.0
M	53	—	Metoprolol Nifedipine	Normal	Normal L.V. 90% RCA: LAD	7.0
M	47	20/day	Propranolol	Lateral myocardial ischaemia	Normal L.V. 78% RCA: LAD	5.0
M	51	10/day	Propranolol	Old widespread myocardial infarct	L.V. aneurysm Total occlusion LAD 80% RCA	5.0
M	43	25/day	Atenolol	Normal	Normal L.V. 90% LAD	8.0
M	43	—	Metoprolol	Normal	Normal L.V. 90% LAD	5.3
M	52	—	Metoprolol Nifedipine Preventive CABG	Old inferior myocardial infarct	Normal L.V. Grafts to LAD: RCA RCA occluded. 80% LAD 70% Cx.	4.0
M	58	—	Nifedipine Bumetamide	Old infarct Myocardial infarction +ve exercise test	—	3.45
M	40	7-10/day	Atenolol	Normal ECG +ve exercise test	—	6.0
Mean 48 ± 2						5.2 ± 0.7

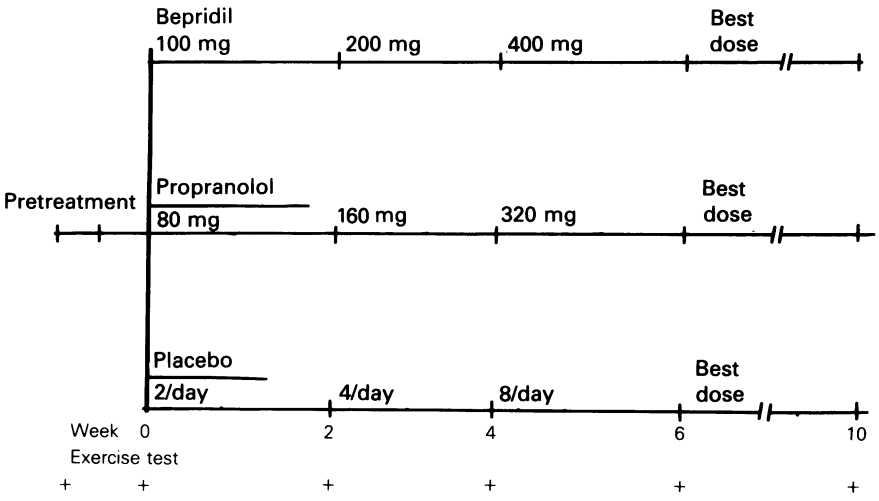

Figure 1 Design of study.

Subjective assessment

A reduction in anginal frequency was noted in all the groups studied but this only reached statistical significance in the bepridil treatment group where an initial mean of 20 ± 7 attacks per 2-week period fell to 10 ± 6 at peak dosage ($P < 0.05$). There was an associated reduction in glyceryl trinitrate consumption in the group from 21 ± 14 to 16 ± 15 on bepridil 400 mg/day.

Exercise capacity

This subjective improvement was associated with improved physical performance. Exercise time until the onset of symptoms was prolonged by bepridil from an initial time of 3.2 ± 0.5 min at entry to 4.0 ± 0.6 min on 100 mg/day ($P < 0.01$). Further improvement in this parameter was observed as the bepridil dosage was increased 4.1 ± 0.5 min on 200 mg/day ($P < 0.01$) and 4.8 ± 0.6 min on the maximum dose of 400 mg/day ($P < 0.001$) respectively (Figure 2). A small but not significant improvement in exercise time was noted in the propranolol group from 5.2 ± 0.7 min at entry to 5.8 ± 1.0 min at the maximum dose prescribed and little change was seen on placebo. Physical work capacity expressed as calculated maximal oxygen uptake (V_{O_2} max) improved in a similar manner with a progressive increase in the bepridil group from a baseline value of 13.1 ± 1.2 ml kg^{-1} min^{-1} to 17.6 ± 1.9 ml kg^{-1} min^{-1} ($P < 0.01$) at 400 mg/day (Figure 3a). As with exercise time there was a modest improvement on propranolol from 17.8 ± 1.1 ml kg^{-1} min^{-1} to 19.6 ± 1.6 ml kg^{-1} min^{-1} at the maximum dose (Figure 3b) and little consistent change on placebo (Figure 3c). The initial improvement on bepridil was once again significant when compared to propranolol ($P < 0.05$). Examining the relative improvement in physical performace between the treatment groups, the percentage increase in physical work capacity was 34% on bepridil and 10% on propranolol. For the first 6 weeks of the study, the improvement on placebo was only 3%. However, because of marked improvement in two patients in the latter phase of the study, the overall improvement in physical work capacity in placebo treated patients was 13%.

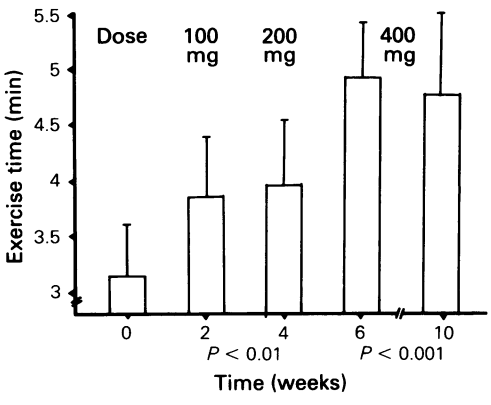

Figure 2 Exercise duration (min) in patients on bepridil at different dose levels.

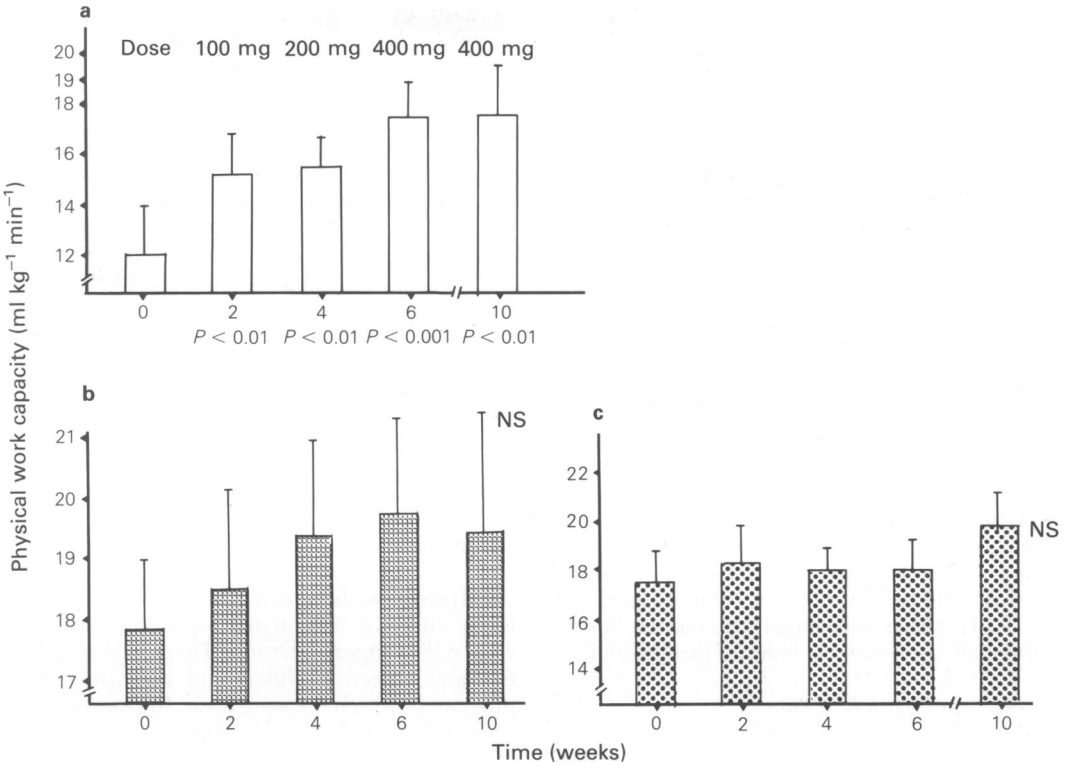

Figure 3 Physical work capacity (ml kg^{-1} min^{-1}) in patients on (a) bepridil (b) propranolol and (c) placebo throughout the study.

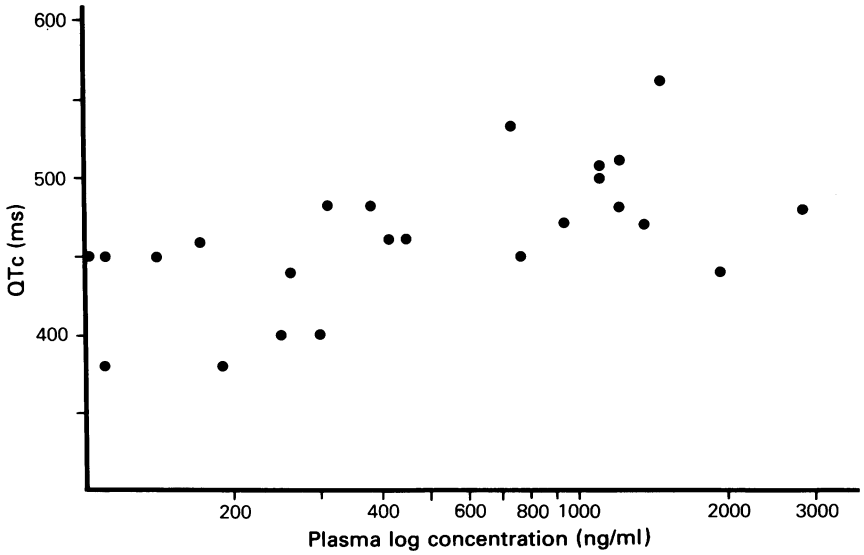

Figure 4 Plot of QTc (ms) and plasma concentration (ng/ml) of bepridil demonstrating no significant correlation. $r = 0.47$.

Haemodynamic variables

As expected bepridil produced a modest reduction in resting heart rate from 74 ± 4 beats/min to 67 ± 3 beats/min on 400 mg/day. There was a reduction of similar magnitude in exercise induced tachycardia where an initial maximal heart rate of 116 ± 5 beats/min fell to 111 ± 5 beats/min on the maximum bepridil dosage. A reduction in heart rate of statistical significance was seen only in the propranolol treatment group where resting heart rate fell from 72 ± 5 to 53 ± 2 beats/min ($P < 0.01$) and the heart rate on exercise reduced from 131 ± 4 to 95 ± 6 beats/min ($P < 0.001$). There was no significant change in this variable on placebo.

No significant changes in systolic or diastolic blood pressure either at rest or on exercise were noted in any of the groups studied but there was a significant reduction in the double product of heart rate × systolic blood pressure which fell on exercise in the propranolol group from 21.5 ± 1.2 × 10^3 to 13.9 ± 1.3 × 10^3 mm Hg/min ($P < 0.01$) which was largely accounted for by attenuation of exercise induced tachycardia.

Electrocardiographic changes

Although no significant changes in the configuration of the surface electrocardiogram were noted on propranolol or placebo, the administration of bepridil led to moderate prolongation of the absolute QT interval. Correcting this for heart rate change to obtain the corrected QT interval (QTc) demonstrated that the change in this variable was independent of the negative chronotropic effect of bepridil. There was widespread individual variation in the QTc response and thus a poor correlation between the QTc interval and bepridil plasma levels ($r = 0.47$) (Figure 4). The degree of QTc lengthening appeared to be dose-related and was maximal when bepridil was increased to 420 mg daily but this increase was modest with an average maximal increase of 27%.

Patient compliance

Patient compliance was good as judged from tablet counts and plasma drug assays. The mean plasma levels of bepridil at each dose range were 159 ± 19 ng/ml, 373 ± 85 ng/ml, 1150 ± 298 ng/ml and 1388 ± 137 ng/ml with the 400 g/day dose.

Adverse effects

No abnormality was found on routine biochemical or haematological testing either before or after drug administration and no patient reported any adverse effects which could be attributed to study medication.

Nine patients failed to complete the protocol. Two patients failed to comply and declined to attend for follow-up. One patient on bepridil 50 mg twice daily suffered primary ventricular fibrillation before exercise when he attended for review at 2 weeks. He was successfully resuscitated and made an uneventful recovery and subsequent coronary angiography demonstrated severe triple vessel disease. Four patients developed unstable angina necessitating their withdrawal, two patients on propranolol and two on placebo. Two patients on propranolol developed rectal bleeding for which no apparent cause was found.

Discussion

In this study we have demonstrated that bepridil is an effective anti-anginal agent in patients with stable angina pectoris. There was subjective and objective evidence of increasing improvement with increasing dose. In comparison with propranolol, bepridil appears to be more effective although between group comparison was limited by the difference in baseline performance despite randomisation. In the bepridil group of patients the mean time to angina was significantly less than in the propranolol group of patients, although in other respects there was comparability between the two groups. Although this potential problem must be accepted with a parallel group study a trial design of this nature largely ameliorates the errors in assessment of exercise capacity due to the training effect which occurs with repeated estimations using a method of exercise initially unfamiliar to the patient (Davies & Sargeant, 1975). The spontaneous improvement in two patients receiving placebo especially in the latter phase of the study, tends to detract from the benefit produced by active medication but this cannot be allowed for in design of antianginal trials (McGraw *et al.*, 1981).

The progressive improvement in exercise performance, as bepridil was increased to 400 mg/day, suggests that this improvement was dose related. Whether 400 mg/day of bepridil (the maximum dosage employed in this study) reflects the plateau of a dose response curve and that further improvement with increasing dose would not be obtained is not known although a recent report suggests the optimum dose probably lies between 300 mg and 400 mg/day (Di Bianco *et al.*, 1983).

The modest reduction in heart rate with bepridil noted in this study is similar to that previously reported (Canicave *et al.*, 1980). The mechanism of this is thought to be due to a direct action on pacemaker cells of the sino-atrial node with reduction in automaticity secondary to Ca^{++} slow channel blockade (Winslow & Kane, 1980; Beaughard *et al.*, 1982). Bepridil has been shown to attenuate both sympathomimetic induced tachycardia and the tachycardia induced by either glucagon or theophylline (Cosnier *et al.*, 1977). In addition to being non-specific, this sympathetic antagonism is non-competitive and independent of any interaction with the β-adrenoceptor. In this respect bepridil is similar to verapamil and diltiazem, whereas nifedipine, which has no sympathetic antagonism, tends to produce an increase in heart rate because of the unopposed sympathetic response to peripheral vasodilatation (Singh *et al.*, 1983). Unlike verapamil which depresses atrio-ventricular conduction bepridil appears to exert little effect on the atrioventricular node even at high doses (Cosnier *et al.*, 1977).

The anti-anginal property of β-adrenoceptor blocking agents is primarily related to the induction of bradycardia and relative hypotension with resultant reduction in myocardial oxygen consumption (McDevitt, 1979). This is reflected in a reduction in the rate-pressure product noted in the propranolol group in this study. With bepridil, however, no significant change was noted which suggests that a major component of the anti-anginal property of bepridil is not related to a reduction in myocardial oxygen consumption. Bepridil has been shown to be a coronary vasodilator (Harder & Sperelakis, 1981) and to increase coronary blood flow in the anaesthetised dog (Cosnier *et al.*, 1977; Marshall & Muir, 1981). Human studies have suggested that the coronary haemodynamic effects of bepridil are similar to those of nifedipine (Merillon *et al.*, 1981) and it seems likely therefore that coronary vasodilatation may be an important factor in the benefits produced by bepridil. Similar results have been found in patients with coronary heart disease.

The electrocardiographic changes induced by bepridil and noted in this study have been reported previously. Although we recorded only moderate prolongation of the QT interval, others have documented minor T-wave changes in addition (Desoutter & Haiat, 1980; Canicave *et al.*, 1980). The precise mechanism of these electrocardiographic changes remains to be determined but may in part be associated with prolongation of ventricular action potential duration (Kane & Winslow, 1980). As with quinidine, there is a large variation in individual patient response but the degree of QT prolongation does appear to be dose related. It is interesting to note that similar electrocardiographic changes are seen with perhexiline and amiodarone (Boucher & Duchene-Marullaz, 1978) both of which can induce bradycardia and reduce myocardial oxygen consumption. Pronounced QT prolongation can be associated with syncope and sudden death but the patient in this study who was resuscitated from ventricular fibrillation had a normal QT interval.

In summary, this study demonstrates that bepridil can produce both subjective and objective improvement in patients with stable angina pectoris secondary to coronary artery disease and the possible mechanisms have been discussed. No adverse effects were noted when doses up to 400 mg/day were prescribed over a 10 week period but further clinical studies are clearly indicated to establish the place of this novel calcium channel blocker in the management of patients with coronary heart disease.

References

Beaughard, M., Ferrier, M., Labrid, C., Lamar, J. C., Leboeuf, J. & Piris, P. (1982). Studies on the bradycardia induced by bepridil. *Br. J. Pharmac.*, **75**, 293–300.

Blomqvist, C. G. (1973). Exercise testing in rheumatic heart disease. *Cardiovasc. Clinics*, **5**, 267–287.

Boucher, M. & Duchene-Marullaz, P. (1978). Comparative effects of amiodarone, perhexiline and bepridil on the cardiac rhythms of the unanaesthetised dog under chronic heart block. *Arch. int. Pharmacodyn. Ther.*, **233**, 65–75.

Canicave, J. C., Deu, J., Jacq. J. & Paillet, R. (1980). Un nouvel antiangoreux, le bepridil. Appreciation de son efficacite per l'epreuve d'effort au course d'un essai a double insu contre placebo. *Therapie*, **35**, 607–612.

Cosnier, D., Duchene-Marullaz, P., Rispat, G. & Streichenberger, G. (1977). Cardiovascular pharmacology of bepridil. A new potential anti-anginal compound. *Arch. int. Pharmacodyn. Ther.*, **225**, 133–151.

Davies, C. T. M. & Sargeant, A. J. (1975). Effects of training on the physiological response to one- and two-leg work. *J. appl. Physiol.*, **38**, 377–381.

Desoutter, P. & Haiat, R. (1980). Modifications electrocardiographiques induites per le bepridil. Un nouvel inhibiteur calcique. *Arch. Mal. Coeur*, **73**, 1237–1238.

Di Bianco, R., Alpert, J., Kataz, R. J., Spann, J.,

Chesler, E., Ferri, D. P., Larca, L. J., Costello, R. B., Nugent, M. E. & Eisenman, M. (1983). Antianginal efficacy of bepridil, a new long acting calcium channel blocker: Results of a 10-week, multicenter, placebo controlled study. (abstr.) *J. Am. Coll. Cardiol.*, **1**, 692.

Gobel, F. L., Nordstrom, L. A., Nelson, R. R., Jorgensen, C. R. & Wang, Y. (1978). The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation,* **57**, 549–556.

Greenblatt, D. J. & Koch-Weser, J. (1974). Adverse reactions to beta adrenergic receptor blocking drugs: A report from the Boston Collaborative Drug Surveillance Programme. *Drugs,* **7**, 118–129.

Harder, D. R. & Sperelakis, N. (1981). Bepridil blockade of Ca^{++} -dependent action potentials in vascular smooth muscle of dog coronary artery. *J. cardiovasc. Pharmac.*, **3**, 906–914.

Kane, K. A. & Winslow, E. (1980). Antidysrhythmic and electrophysiological effects of a new anti-anginal agent, bepridil. *J. cardiovasc. Pharmac.*, **2**, 193–203.

Marshall, R. J. & Muir, A. W. (1981). The beneficial actions of bepridil in acute myocardial infarction in anesthetised dogs. *Br. J. Pharmac.*, **73**, 471–479.

McDevitt, D. G. (1979). Adrenoreceptor blocking drugs: Clinical pharmacology and therapeutic use. *Drugs*, **17**, 267–288.

McGraw, B. F., Hemberger, J. A., Smith, A. L. & Schroeder, J. S. (1981). Variability of exercise performance during long-term placebo treatment. *Clin. Pharmac. Ther.*, **30**, 321–327.

Merrillon, J. P., Duffloux, M. A., Eustigneff, T., Pansard, Y., Guiomard, A., Zygelman, M., Aumont, M. C. & Gourgon, R. (1981). Modifications hemodynamiques et coronaires induites par differents inhibiteurs des canaux lents dans l'insuffisance coronaire chronique: la nifedipine, le verapamil et le bepridil. *Therapie,* **36**, 123–124.

Packer, M., Meller, J., Medina, N., Yshak, M., Smith, H., Holt, J., Guererro, J., Todd, G. D., McAllister, R. G. & Gorlin, R. (1982). Haemodynamic consequences of combined β-adrenergic and slow calcium channel blockade in man. *Circulation,* **65**, 660–668.

Robinson, B. F. (1967). Relation of heart rate and systolic blood pressure to the onset of angina pectoris. *Circulation,* **35**, 1073–1083.

Singh, B. N., Nademanee, K. & Baky, S. H. (1983). Calcium antagonists. Clinical use in the treatment of arrhythmias. *Drugs,* **25**, 125–153.

Tweddel, A. C., Beattie, J. M., Murray, R. G. & Hutton, I. (1981). The combination of nifedipine and propranolol in the management of patients with angina pectoris. *Br. J. clin. Pharmac.*, **12**, 229–233.

Vaughan-Williams, E. M. (1970). Classification of anti-arrhythmic drugs. *Symposium on Cardiac Arrhythmias*, eds Sandee, E., Flensted-Jensen, E. & Oleson, K. H. pp. 449–472. Sweden: AB Astra Sodertalje.

Vogel, S., Crampton, R. & Sperelakis, N. (1979). Blockade of myocardial slow channels by bepridil (CERM 1978). *J. Pharmac. exp. Ther.*, **210**, 378–385.

Winslow, E. & Kane, K. A. (1981). Supraventricular antidysrhythmic and electrophysiological effects of bepridil, a new antianginal agent. *J. cardiovasc. Pharmac.*, **3**, 655–667.

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