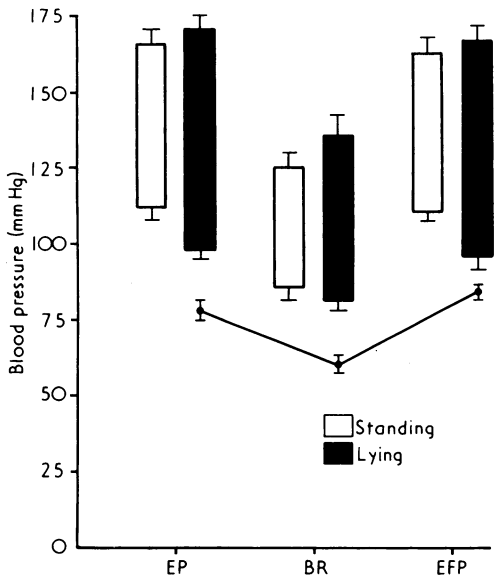

FIG 6—Effect of return to placebo tablets on pulse rate and blood pressure in 12 patients. EP = End of placebo run-in period. BR = Best response during active treatments. EFP = End of final placebo period.

It has been suggested that patients with essential hypertension may fall into three groups[8]: those with high renin levels, who respond best to beta-blockers; those with low renin levels, who respond best to diuretics; and those with normal renin, who respond equally to beta-blockers or diuretics. We could not identify any such subgroups in these few patients or any biochemical of physical marker that could have predicted a response to a diuretic or beta-blocker. Certainly atenolol had a greater hypotensive effect than bendrofluazide in some patients, but an equal number did better with bendrofluazide than with atenolol. This difference in response bore no relation to the hyporeninaemic effect of atenolol.

The decision to include patients with severe hypertension in a trial incorporating a placebo period was not taken lightly. Most of the patients in the trial were referred to us because they were not being controlled satisfactorily on existing regimens and it was not clear whether this was due to the regimens themselves or to lack of patient compliance. We regarded it as essential to establish the true level of untreated blood pressure and the degree of patient compliance by having a closely supervised placebo period and incorporating a riboflavin marker into one of the tablets. We found that the pressure levels recorded during our placebo period differed little from those achieved when the patients were on their previous "treatment" regimens.

The agent of first choice for treating hypertension is likely to depend on many factors. So far as atenolol and bendrofluazide are concerned there was no significant difference in their effect on systolic blood pressure, although atenolol was more effective than bendrofluazide on diastolic blood pressure ($P < 0.05$). The biochemical effects produced by the two agents may, however, be important in deciding which should be regarded as first-choice treatment. The acute and long-term effects of bendrofluazide (hypokalaemia, hyperuricaemia, and a tendency towards hyperglycaemia) are well known but are clinically not important. The long-term effects of atenolol are not yet known but it appears to have several, possibly advantageous biochemical effects—for example, reduction in plasma renin, a slight increase in serum potassium, and a small reduction in urate. It remains to be seen whether atenolol confers the same benefit in respect of myocardial infarction as has been shown with practolol[9] and alprenolol.[10,11]

Drugs and matching placebos were kindly supplied by the Boots Company Limited, Ciba, and ICI Limited. Renin measurements were made by Dr David Craven in the professorial department of obstetrics and gynaecology of the City Hospital, Nottingham.

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Increased exercise tolerance with nitrates in beta-blockaded patients with angina

R H BAXTER, I M LENNOX

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Summary

In 14 beta-blockaded anginal subjects, 10 of whom had poor left ventricular function, sublingual isosorbide dinitrate significantly increased maximal exercise capacity on a standardised multistage treadmill test. This was associated with changes in heart rate and blood pressure suggestive of a fall in left ventricular work.

The effect of isosorbide lasts for at least two hours and when taken before exercise may be a useful addition to beta-blockade in patients with angina.

Cardiac Department, Victoria Infirmary, Glasgow G42 9TY
R H BAXTER, MB, MRCP, senior registrar
I M LENNOX, MB, MRCP, registrar

Introduction

Beta-blockers are now established in the medical management of angina pectoris. Their beneficial effects, which include increased exercise tolerance and decreased frequency of anginal attacks,[1-3] are continuous throughout the day. The clinical response to beta-blockade may be partial as some patients still have limiting angina. Furthermore, these drugs diminish con-

tractility and increase the volume of the left ventricle.[4] In contrast nitrates reduce left ventricular end-diastolic and pulmonary pressure[5] and may improve contraction of dyskinetic areas of ischaemic myocardium.[6 7] Thus on theoretical grounds a combination of the two drugs might be beneficial, though few studies have examined this.

This study was designed to test the effects of isosorbide dinitrate given to patients with angina pectoris already receiving treatment with beta-blockers, by testing the change in maximal exercise tolerance.

Patients and methods

The study was carried out on 14 men aged under 65 (mean 52±9). All patients had had angina of effort for at least three months which had become stable but persistent in spite of beta-blockers. Nine patients were being treated with propranolol (mean daily dosage 153±81 mg), four patients with oxprenolol (mean daily dosage 280±69 mg), and one patient with acebutolol (600 mg daily). In addition to history and clinical examination, chest *x*-rays and 12-lead resting electrocardiograms (ECGs) were recorded. Four patients had a history of previous myocardial infarction, supported by ECG and enzyme changes. Resting 12-lead ECG at the time of the current study was normal in six patients; four had pathological Q waves of myocardial infarction—one of whom had right bundle branch block, and four ST-T changes of myocardial ischaemia.

Selective coronary arteriography and left ventricular angiography carried out on 10 patients considered for coronary bypass surgery, showed areas of dyskinesia in the left ventricle in eight. Mean left ventricular end-diastolic pressure was 20±9 mm Hg, and all 10 had significant coronary occlusion (that is, >50% narrowing). On this basis two patients had triple, seven double, and one single vessel disease.

The standardised multistage exercise test[8] was performed on a treadmill (Quinton instruments) with continuous monitoring of heart rate and ECG from a modified chest lead (V5). In this test the end-point of maximum tolerated effort is a measure of physical capacity which is reproducible in each patient with stable angina.[8] The studies were performed at least two hours after meals and at least one baseline test was performed in each patient to familiarise him with the equipment. Patients were accepted into the study only if their exercise was limited by angina, the end-point of maximal physical capacity reproducible, and if either the coronary arteriogram showed occlusive disease or the ECG was ischaemic—that is, pathological Q waves, T inversion, or S-T depression (>1 mm for >0·08 s). Heart rate, ECG (modified V5 lead), and cuff blood pressure were recorded at rest, at the end of each three-minute stage, and, at the exercise end-point, the onset of angina.

The objective was to test the effect of sublingual nitrate on the maximal exercise capacity of these beta-blockaded subjects. The patients, all of whom continued with their oral beta-blocker, were divided into two groups. In group 1 (six patients), placebo effect was tested by comparing three normal exercise tests. In each the results of a test while taking the beta-blocker alone were compared with those of two subsequent tests, one after the addition of a sublingual placebo and one after 5 mg sublingual isosorbide dinitrate. In group 2 (eight patients) the results of a test while taking the beta-blocker alone were compared with those of a subsequent test after adding 5 mg sublingual isosorbide dinitrate. The treadmill tests were performed in each patient on the same day, 10 minutes after drug or placebo administration with 15 minutes' rest between studies. The two groups of patients did not differ in respect of age, extent of coronary disease, left ventricular end-diastolic pressure, or frequency of dyskinesia. Statistical comparisons were made using the paired *t* test.

Mean (±SD) heart rate and systolic blood pressure at rest and at peak exercise

	Resting pre-exercise		Peak exercise (ie, end-point)	
Drug treatment:	Beta-blocker	Beta-blocker and isosorbide	Beta-blocker	Beta-blocker and isosorbide
Heart rate (beats/min)	73 (±13)	84 (±15)*	109 (±16)	113 (±16)
Systolic blood pressure (mm Hg)	136 (±19)	123 (±12)*	160 (±26)	140 (±29)†

*P<0·001. †P<0·05.

Results and comment

In maximal treadmill testing (figs 1 and 2) the mean exercise time to onset of angina after sublingual isosorbide for patients in group 1 was 267 (±94) s, a significant increase over the mean time of 186 (±101) s recorded after sublingual placebo (P<0·05). When the same patients were tested without any additional treatment to the long-term beta-blockade, the mean exercise time was 179 (±98) s, not significantly different from the times recorded after additional sublingual placebo.

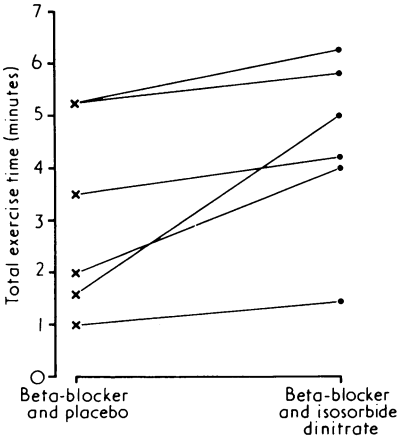

FIG 1—Comparison between individual responses to sublingual isosorbide dinitrate as opposed to placebo, in beta-blockaded subjects (group 1). Mean exercise time to angina 267 (±94) s after 5 mg isosorbide dinitrate showed a significant increase over mean time of 186 (±101) s after placebo (P<0·05).

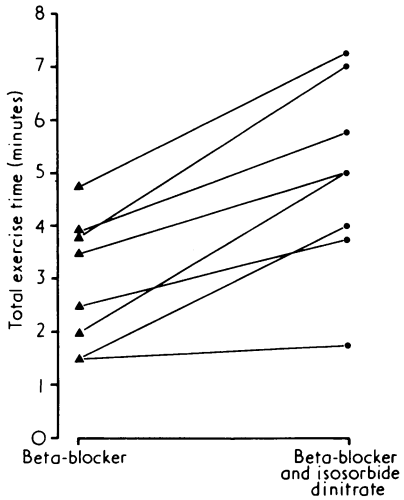

FIG 2—Improvement in mean maximal exercise time with isosorbide dinitrate in beta-blockaded subjects (group 2). Mean of 296 (±101) s with isosorbide dinitrate was significantly greater than mean of 176 (±69) s recorded when no additional treatment was given (P<0·001).

In patients in group 2 the mean maximal exercise time of 296 (±101) s after the isosorbide was also significantly greater than the mean time of 176 (±69) s recorded with the beta-blocker alone (P<0·001). The placebo used in group 1 produced no significant change in heart rate or systolic blood pressure, but on combining the results (table) for all 14 patients (groups 1 and 2) of the effect of the nitrate there was a significant increase (P<0·001) in resting heart rate, from 73 (±13) to 84 (±15) beats/min, and a significant (P<0·001) fall in systolic blood pressure, from 136 (±19) to 123 (±12) mm Hg.

At the maximal exercise point in tests on patients taking the beta-blocker plus nitrate the systolic blood pressure was significantly lower and the heart rate slightly higher than in those taking the beta-blocker alone. Consequently the product (heart rate × systolic blood pressure) was also lower (15 820 compared with 17 440), implying a reduction in myocardial work during the nitrate tests. In no patient was maximal exercise capacity diminished by the nitrate, while in seven out of 14 the increase was greater than 50%.

Discussion

Nitrates act in angina by reducing both left ventricular preload (venous pressure) and after-load (blood pressure), both of which are determinants of myocardial work. The effect is that both diastolic pressure and volume as well as wall tension in the left ventricle are reduced, thereby diminishing myocardial oxygen consumption.[5] Further benefits are increased coronary blood flow to the ischaemic myocardium[9] and improved contraction of dyskinetic area in the left ventricle.[6]

Numerous studies have shown the value of beta-receptor blocking agents in increasing exercise tolerance and reducing anginal attacks.[1-3] In contrast to nitrates, these drugs act by reducing the sensitivity of the myocardium to catecholamines during exercise and emotion, thereby reducing both the resting and exercise heart rate. They also reduce myocardial contractility and these two factors lower myocardial oxygen requirement.[4]

These effects are counteracted by an increase in left ventricular end-diastolic pressure and wall tension, and, even though overall cardiac performance is usually improved in anginal subjects, not all patients derive relief from beta-blockade —even when the dose is adjusted to reduce the peak exercise as well as the resting heart rate.[10]

Few studies have tested the possible synergestic effect of beta-blockers and nitrates. Russek[11] reported increased exercise tolerance after propranolol and isosorbide, but this was not confirmed by Aronow,[12] although timing of his exercise tests after nitrate administration, may have produced the results. Weiner[13] in a detailed haemodynamic study reported improved exercise tolerance with reduction in left ventricular end-diastolic pressure in anginal subjects given intravenous propranolol plus sublingual glyceryl trinitrate, compared with a propranolol treated group.

In our study exercise tolerance was significantly increased by adding isosorbide to the patients already on beta-blockers, most of whom (eight out of the 10 studied) had either raised left ventricular end-diastolic pressure or dyskinetic areas of ventricle. Probably in them nitrates improved exercise tolerance by decreasing left ventricular work as a result of the fall in blood pressure and presumably left ventricular end-diastolic pressure.

The use of sublingual nitrates is often limited by their short action, and people still disagree about the role of rapid hepatic degradation of orally administered long-acting preparations in this effect. The effect of sublingual isosorbide dinitrate administered sublingually lasts for at least two hours[14 15] and when taken by patients with angina before exercise may be a useful addition to beta-blockade.

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Amoxycillin and co-trimoxazole in presumed viral respiratory infections of childhood: placebo-controlled trial

BRENT TAYLOR, G D ABBOTT, M McK KERR, D M FERGUSSON

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Summary

A double-blind randomised controlled trial of amoxycillin, co-trimoxazole, and placebo was conducted on 197 children presenting with presumed viral respiratory infections. Routine throat swabs were taken to exclude streptococcal disease. The three disease categories studied—nasopharyngitis, pharyngotonsillitis, and bronchitis (including laryngotracheobronchitis)—showed a generally similar pattern of resolution irrespective of treatment.

Nevertheless, seven out of 66 children receiving placebo were withdrawn from the trial with unremitting symptoms or complications thought to require antimicrobial treatment. Only two of 56 children receiving amoxycillin and none of 75 receiving co-trimoxazole were withdrawn. Three other children receiving amoxycillin and three receiving placebo were seen during the trial but further treatment was not thought to be necessary. Thus the return consultation rate in children receiving placebo therapy was 15% compared with 4% for those receiving antimicrobial treatment. Antimicrobial treatment was associated with less nasal discharge on the eighth day of treatment. Placebo treatment allowed an earlier return to normal activity. There was a high incidence of possible side effects on all regimens including placebo.

It is concluded that the benefits of antimicrobial treatment in presumed viral respiratory infections are marginal, and they should not be routinely prescribed for these conditions.

Department of Paediatrics, The Christchurch Clinical School, Christchurch Hospital, Christchurch, New Zealand
BRENT TAYLOR, MRCP, MRACP, senior lecturer
G D ABBOTT, MD, FRACP, senior lecturer
D M FERGUSSON, BA, research officer

St Albans Medical Centre, Christchurch, New Zealand
M McK KERR, DOBST, MNZCGP, general practitioner