

Comparative Clinical Trial of Oxymfedrine And Oxprenolol In Patients With Angina Pectoris

N. NAQVI*

R.C.P. GRAHAM**

ABSTRACT

Oxymfedrine, a new anti-anginal drug with a unique mode of action, was compared with placebo and oxprenolol in thirty patients with stable angina pectoris. Total exercise time and exercise time to onset of angina was significantly improved, compared to placebo and was comparable to that produced by oxprenolol. Heart rate and blood pressure were not affected. Side effects were few.

INTRODUCTION

Over the past decade much advance has been made in the treatment of angina pectoris. Although coronary artery bypass surgery is the therapy of choice in certain sub-groups of patients with angina, in the vast majority medical therapy is used initially and surgery resorted to only in those cases where full medical therapy has failed to control disabling symptoms of angina.

The three major groups of drugs used in the treatment of angina in the United Kingdom are the nitrates, the beta-adrenoreceptor blocking drugs and the calcium antagonists. However, the search for other anti-anginal drugs continues. Recently a new drug, oxymfedrine, (Ildamen, ASTA Pharma AG) has been reported to be an effective treatment of angina (Whittington & Raftery, 1980a; Whittington & Raftery, 1980b). It is an aminoketone of the phenylethylamine series of drugs. There is little experience with this drug in the United Kingdom.

Our study was designed to compare the efficacy and tolerance of oxymfedrine and oxpre-

nolol in patients with stable exertional angina pectoris.

MATERIAL AND METHODS

Thirty consecutive patients with stable angina pectoris seen in the Cardiology Clinic were enrolled into the trial. The patients gave written consent and the Hospital Ethics Committee approved the protocol. All the patients had typical symptoms of effort induced angina, had normal resting electrocardiograms and had evidence of cardiac ischaemia on exercise. Apart from nitrates they had not received any other anti-anginal therapy.

Patients with unstable angina or recent myocardial infarction were excluded from the trial, as were those with bronchial asthma or history of bronchospasm, cardiac failure, valvular heart disease and women at risk of pregnancy. Patients not in sinus rhythm or those whose electrocardiogram showed abnormalities of QRS complex or ST segment at rest were also excluded.

The trial design was double-blind, randomised, cross-over trial, comparing oxprenolol and oxymfedrine with an unrandomised, single-blind placebo run-in period. The dose of oxymfedrine was 24 mg qid and that of oxprenolol was 80 mg qid. All patients received simultaneously two different sets of tablets, each taken four times daily; one had the appearance of oxymfedrine and the other that of oxprenolol. According to the randomisation code, at any time one of these two medications would consist of active drug and the other inactive placebo. During the placebo run-in phase patients received placebo drugs of both types. Accordingly, from the patient's point of view medication remained unaltered throughout the entire trial period.

*Consultant Physician

**Clinical Assistant

Department of Cardiology Royal Albert Edward Infirmary Wigan
WNI 2NN Greater Manchester United Kingdom

All exercise tests were carried out on a Quinton treadmill utilising the Bruce protocol (Bruce & Nornsten, 1969). Continuous electrocardiographic monitoring was performed on Marquette 3500 exercise module and electrocardiograms were recorded before the exercise test, at the end of each three minute stage of the protocol and at the end of the exercise test. Electrocardiograms were recorded every minute in the post exercise phase for at least six minutes or until the ST segment returned to the isoelectric line, whichever was the longer. For each patient, exercise tests were performed at approximately the same time of day on every occasion. Blood pressure was recorded immediately prior to the commencement of the exercise, at the end of each stage and at the end of the exercise test. Time to onset of angina was noted in each patient. In every case the exercise was terminated due to chest pain and/or tightness.

On entry into the trial, an initial "pre-trial" exercise test was performed. All patients then underwent an initial two-week placebo run-in period known to the investigator, but not to the patient. At the end of this period, a further exercise test was performed after which the patients proceeded to the main randomised, double-blind, crossover phase of the trial. This consisted of six-week periods of active treatment either with oxyfedrine or oxprenolol according to a pre-determined randomised code. At the end of each six-week treatment period an exercise test was performed. At the time of each exercise test patients were questioned regarding any side effects and subjective response to the drug.

During the trial the patients did not have any other drugs apart from the trial drug and glyceryl trinitrate.

Statistical analysis is by Student's "t" test for paired observation, each patient acting as his own control. $P < 0.05$ is considered significant. Values are expressed as mean \pm standard error.

RESULTS

Thirty patients entered the trial (nineteen males and eleven females). Their mean age was 52.3 years (range 37-65), mean weight was 74.3 kg (range 51-104), mean height was 169.1 cm (range 150-187) and mean body surface area was

1.83 m² (range 1.57-2.10). Of these, five patients (three males and two females), failed to complete the trial. One developed electrocardiographic evidence of asymptomatic subendocardial myocardial infarction during the placebo run-in period. Three patients were withdrawn during oxprenolol therapy, one due to development of intermittent claudication and two due to gastric intolerance to oxprenolol. One patient was withdrawn during oxyfedrine therapy because of increasing angina pectoris and general malaise.

The remaining twenty-five patients completed the trial and their results are as follows:

1. Total exercise time in minutes (figure 1).

Pre-trial total exercise time was 6.07 ± 0.45 and at the end of placebo run-in 5.94 ± 0.47 . The difference between these two periods was not significant. There was a significant increase in total exercise time with both active drugs. oxyfedrine increased the exercise time to 6.92 ± 0.46 ($p < 0.02$ compared to pre-trial period and $p < 0.01$ compared to placebo run-in period).

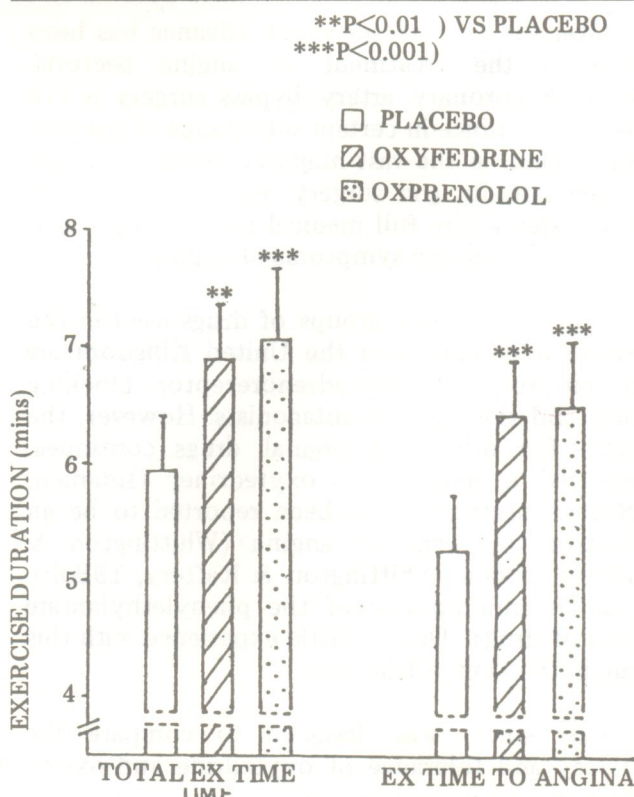


Figure 1

Total exercise time and time to onset of angina.

Oxprenolol increased exercise time to 7.09 ± 0.58 ($p < 0.01$ compared to pre-trial period and $p < 0.001$ compared to placebo run-in period). The difference between the two active drugs was not statistically significant.

2. Exercise time to onset of angina, in minutes (figure 2).

This value for the pre-trial period was 5.44 ± 0.47 and for placebo run-in period was 5.27 ± 0.48 . The difference between the two values was not significant. Oxyfedrine increased exercise time to onset of angina to 6.45 ± 0.45 significantly better than pre-trial period ($p < 0.01$) and placebo run-in period ($p < 0.01$). Similar increase was noted with oxprenolol 6.52 ± 0.56 significantly better than pre-trial period ($p < 0.001$) and placebo run-in period ($p < 0.001$). There was no significant difference between the two active drugs.

3. Heart rate per minute (figure 2).

There was no significant difference in the heart rate at rest and at peak exercise between the pre-trial period, placebo run-in period and oxyfedrine ($86.5 \pm 3.1 - 147.1 \pm 4.3, 87.4 \pm 2.9 - 146.8$

$\pm 3.8, 86.1 \pm 2.7 - 146.9 \pm 3.0$ respectively). As expected oxprenolol produced highly significant reduction in heart rate at rest (71.8 ± 2.4) and at peak exercise (126.1 ± 4.3) compared to pre-trial period ($p < 0.001$), placebo run-in period ($p < 0.001$) and oxyfedrine ($p < 0.001$).

4. Systolic blood pressure, in mm Hg (figure 3).

There was a slight, statistically insignificant reduction in systolic blood pressure at rest with oxyfedrine (137.8 ± 3) compared to pre-trial period (142.8 ± 3.5) and placebo run-in period (140.4 ± 2.9). Oxprenolol produced a significant reduction in resting blood pressure 134.0 ± 2.4 compared to pre-trial period ($p < 0.01$) and placebo run-in period ($p < 0.02$) but not to oxyfedrine therapy (N S). Peak exercise systolic blood pressure was not significantly different during all four periods—pre-trial period 178.8 ± 4.8 , placebo run-in period 178.0 ± 4.8 , oxyfedrine 175.2 ± 4.9 and oxprenolol 169.2 ± 4.0 .

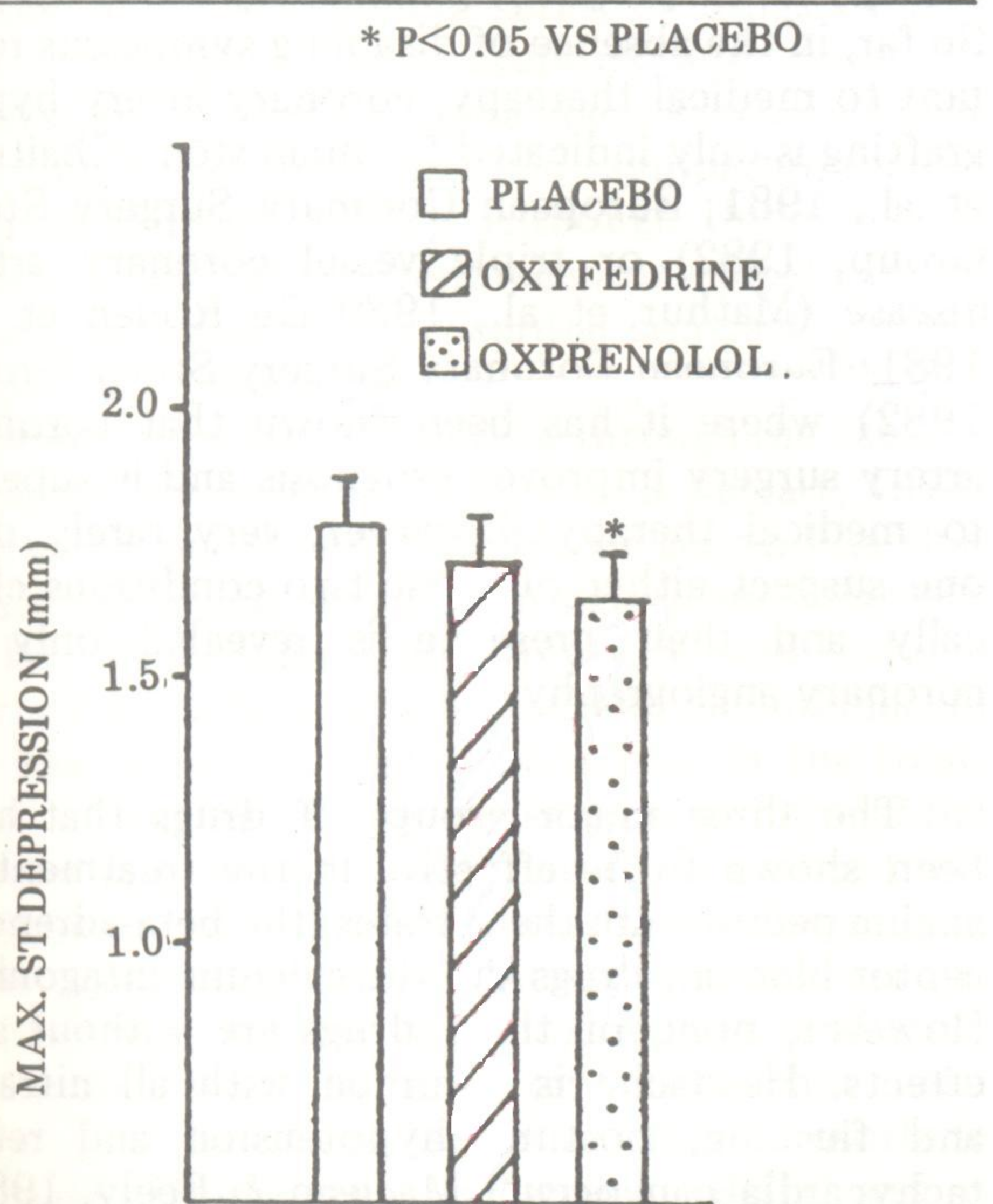


Figure 2

Heart rate at rest and at peak exercise.

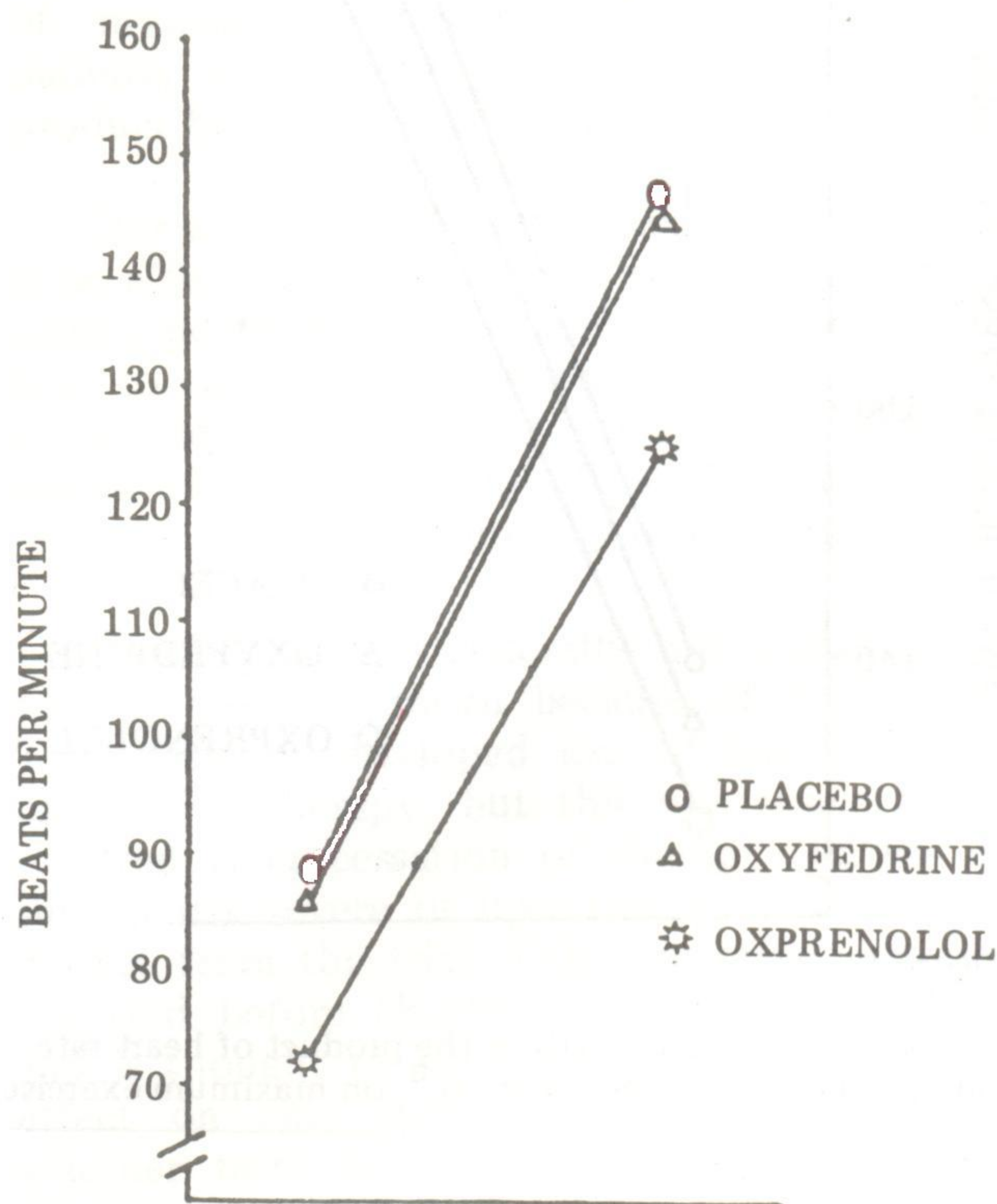


Figure 3

Systolic blood pressure at rest and at peak exercise.

5. Diastolic blood pressure.

The diastolic blood pressure at rest and on peak exercise during all four periods was similar and the changes were not statistically significant.

6. Double product $\times 10^{-3}$ (figure 4).

Double product, product of systolic blood pressure and heart rate at peak exercise, was significantly less for oxprenolol (21.4 ± 1.0) compared to both placebo (26.1 ± 1.1) and oxyfedrine (25.9 ± 1.1). There was no significant difference in this value between oxyfedrine and placebo.

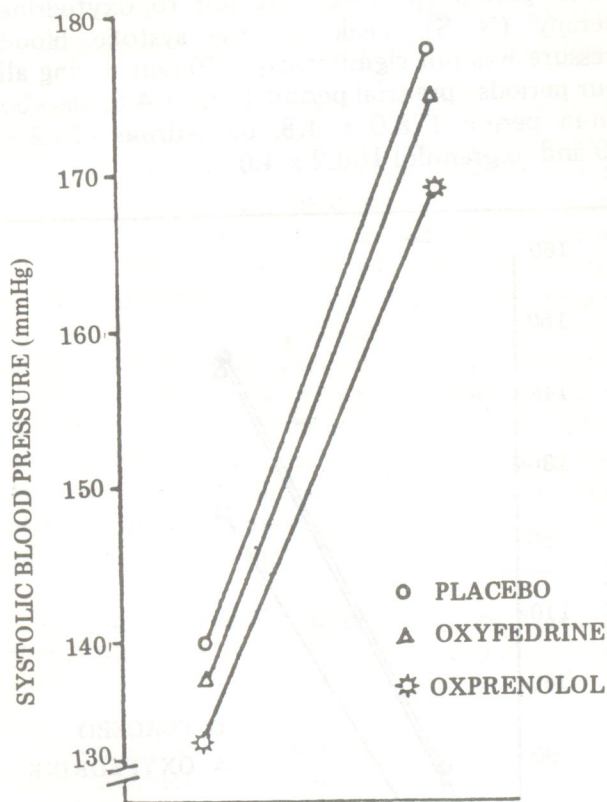


Figure 4

Double product $\times 10^{-3}$ — the product of heart rate and systolic blood pressure $\times 10^{-3}$, on maximum exercise.

7. Side effects.

Two patient reported loss of taste during oxyfedrine therapy. Immediately after cessation of therapy taste returned to normal in both. One patient reported each of headache, malaise, gastro-

intestinal disturbance, dry mouth, insomnia and cramp. These symptoms were mild, not upsetting and no patient was withdrawn from the trial solely because of side effects to oxyfedrine therapy. One patient who complained of nausea was withdrawn from the trial because of increasing angina and not nausea. There were no arrhythmias noted during oxyfedrine therapy.

With oxprenolol therapy, two patients complained of intermittent claudication, one of whom had to be withdrawn from the trial because of this. Three patients complained of gastric disturbance, two having to be withdrawn from the trial because of this. One patient complained of dizziness and one of insomnia.

DISCUSSION

The therapy of angina pectoris in the first instance is medical. Coronary angiography, in this country, is performed only when full medical therapy has failed and the decision has been made to proceed to either coronary artery bypass grafting or coronary angioplasty. It is possible that this practice may change in future, if it is proven that surgical therapy is superior to medical therapy in the prognosis of coronary artery disease. So far, in the absence of disabling symptoms resistant to medical therapy, coronary artery bypass grafting is only indicated for main-stem (Chaitman et al., 1981; European Coronary Surgery Study Group, 1982) or triple vessel coronary artery disease (Mathur et al., 1980 De Rouen et al., 1981; European Coronary Surgery Study Group, 1982) where it has been shown that coronary artery surgery improves prognosis and is superior to medical therapy. However, very rarely does one suspect either of these two conditions clinically and their presence is revealed only by coronary angiography.

The three major groups of drugs that have been shown to be effective in the treatment of angina pectoris are the nitrates, the beta-adrenoreceptor blocking drugs and the calcium antagonists. However, none of these drugs are without side effects. Headache is common with all nitrates, and flushing, postural hypotension and reflex tachycardia can occur (Maclean & Feely, 1983). Unwanted effects of beta-adrenoreceptor blocking drugs are ~~bradycardia, cold hands and feet~~ (Feely et al., 1983) and these drugs are

contra-indicated in obstructive airways disease, incipient or established cardiac failure and peripheral vascular disease. Of the calcium antagonists the two most widely used drugs in this country are verapamil and nifedipine. Verapamil has a negatively inotropic action and this limits its use in certain patients. Although usually well tolerated it can cause constipation, headache, dizziness and rashes (Maclean & Feely, 1983). Nifedipine may worsen angina or cerebral ischaemia in some patients, and in about 6% causes headaches or nausea, flushing and dizziness, which can be severe (Maclean and Feely, 1983). Ankle oedema unresponsive to diuretic therapy may occur (Maclean & Feely, 1983). Moreover, the response to different doses of nifedipine can be highly variable (Dranfield et al., 1983), and a dose of this drug that is beneficial in one patient may have minimal or opposite effects in another. The authors advise caution in administration of nifedipine, and careful titration of doses should be carried out for individual patients to obtain maximum benefit (Dranfield et al., 1983).

Therefore, the search for new anti-anginal drugs continues. Oxymetazoline (Ildamen, ASTA Pharma AG) is one such drug. It is an aminoketone of the phenylethylamine series of drugs. It is a partial agonist at beta-receptors and could be accurately described as a beta-adrenoreceptor blocking drug with marked sympathomimetic activity (Parratt, 1981). Although there is clear evidence of beta-adrenoreceptor blockade in animal experiments, myocardial contractility and output are maintained (Parratt, 1972). It also markedly increases blood flow through the acutely ischaemic myocardium (Marshall & Parratt, 1974) and has a peripheral venodilator action like that of nitroglycerine, resulting in significant decreases in left ventricular filling pressure and volume (Parratt & Mackenzie, 1981). Clearly, combination of these effects is highly beneficial in the treatment of angina. There is decrease in myocardial oxygen requirements resulting from reduced left ventricular end diastolic pressure, volumes and heart size, with marked increase in myocardial blood flow in acutely ischaemic regions of the left ventricular wall. In fact oxymetazoline has been shown to be more effective than isosorbide dinitrate (Whittington & Raftery, 1980a) and as effective as propranolol (Whittington & Raftery, 1980b) in the treatment of angina.

The product of heart rate and systolic blood pressure has been used as an index of myocardial oxygen consumption, and it has been suggested that angina will recur at a particular rate - pressure product in a reproducible manner on repeated cardiac stress (Sowton et al., 1967). However, this has not been borne out in a recent study where William et al. (1985) showed that myocardial oxygen consumption diminished at identical rate - pressure product on repeated cardiac stress. The factor responsible for this phenomenon, they suggested, was adaptation to exercise, or the "warm up phenomenon". Therefore, patients should be able to exercise to a higher rate - pressure product before the onset of angina.

In our study angina occurred at a higher rate - pressure product when the patients were on oxymetazoline compared to the time they were on oxprenolol and identical to that on placebo. Similar findings were obtained in Fananapazir and Bray's study (1985) when they compared oxymetazoline to atenolol. We suggest that in our study oxymetazoline was the factor responsible for reduction of myocardial oxygen consumption allowing patients to exercise to a higher rate-pressure product before onset of angina.

Our study has demonstrated that oxymetazoline is as effective as oxprenolol in the treatment of angina pectoris. Total exercise time and exercise time to onset of angina was significantly improved compared to placebo and was comparable to that produced by oxprenolol. Heart rate and blood pressure were not affected by oxymetazoline.

Oxymetazoline was generally well tolerated. No patient was withdrawn because of side effects. Two patients developed loss of taste while on oxymetazoline therapy, but this was transient and resolved after cessation of therapy. It was not sufficiently severe or upsetting to warrant withdrawal from the trial. This side effect has been reported before (Raftery & Whittington, 1982) and is thought to be due to the drug's transient effect on zinc metabolism. We do not know whether taste would have returned in spite of continuation of therapy.

As yet we do not know what effect oxymetazoline would have in combination with a beta-blocker. Parratt (1981) as shown that oxymetazoline

is a partial agonist at beta-adrenoreceptors and increases myocardial contractility. This action might well nullify the action of beta-blockers and reduce their anti-anginal efficacy. On the other hand it is possible that this may not happen and the anti-anginal effects of oxyfedrine may be complementary to and synergistic with those of beta-blockers, and a combination of these two drugs may be more effective in angina than either alone. Since oxyfedrine is already in daily use in certain countries and may well be used in combination with a beta-blocker, it is imperative that a controlled clinical trial is conducted forthwith to elicit the effects of oxyfedrine in combination with a beta-blocker. Until the results of such a trial are available, we would not advise use of oxyfedrine with a beta-blocker.

In summary oxyfedrine is a new anti-anginal drug with a unique mode of action, different from that of other anti-anginal drugs, is as effective as oxprenolol in the treatment of angina, is well tolerated and has few side effects. It provides a viable alternative to existing forms of anti-anginal therapy and may even be used as a first line drug in the management of angina.

ACKNOWLEDGEMENTS

We thank ASTA Pharma AG of Frankfurt for supplies of tablets and placebo, Dr. R. Kohn and Dr. J. Whittington of Medical Advisory Services (Clinical and General) Limited for organisational assistance and Mrs. J. M. Dalton for secretarial services.

Requests for reprints to Dr. Nayyar Naqvi, Department of Cardiology, Royal Albert Edward Infirmary, Wigan Lane, Wigan, Greater Manchester, United Kingdom.

REFERENCES

- BRUCE, R.A. & NORSTEN, T.R. Exercise testing in evaluation of patients with ischaemic heart disease *Prog. Cardiovasc. Dis.*, 11, 371 (1969).
- CHAITMAN, B.R., FISHER, L.D., BOURASSA, M.G. et al. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease: report of the collaborative study in coronary artery surgery (C.A.S.S.) *Am. J. Cardiol.* 48, 765-777 (1981).
- DE ROUEN, T.A., HAMMERMEISTER, K.E., DODGE, H.T. Comparisons of the effects on survival after coronary artery surgery in subgroups of patients from the Seattle Heart Watch Circulation, 63, 537-545 (1981).
- DRANFIELD, J., WRIGHT, C., FOX, K. Treatment of angina pectoris with nifedipine: importance of dose titration *Brit. Med. J.*, 286, 1467-1479 (1983).
- EUROPEAN CORONARY SURGERY STUDY GROUP Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris *Lancet*, II, 1173-1180 (1982).
- FANANAPAZIR, L. & BRAY, C.L. Comparison of oxyfedrine and atenolol in angina pectoris—a double-blind study *Br. J. clin. Pharmacol.* 20, 405-410 (1985).
- FEELY, J., DE VANE, P.J., MACLEAN, D. Beta-blockers and sympathomimetics *Brit. Med. J.*, 286, 1043-1047 (1983).
- MACLEAN, D. & FEELY, J. Calcium antagonists, nitrates and new anti-anginal drugs *Brit. Med. J.*, 286, 1127-1130 (1983).
- MATHUR, V., S., HALL, R.J., CARCIA, E., DE CASTIO, C.M., Cooley, D.A. Prolonging life with coronary bypass surgery in patients with three vessel disease, *Circulation*, 62, suppl. 1,1-8 (1980).
- MARSHALL, R.J. & PARRATT, J.R. Drug induced changes in blood flow in the acutely ischaemia canine myocardium. Relationship to subendocardial driving pressure *Clin. Exp. Pharmacol. Physiol.*, 1, 99-112 (1974).
- PARRATT, J.R. Oxyfedrine as an anti-anginal agent *Lancet*, I, 441 (1981).
- PARRATT, J.R. The haemodynamic effects of prolonged oral administration of oxyfedrine, a partial agonist at beta-adrenoreceptors: comparison with propranolol *Brit. J. Pharmacol.*, 51, 5-13 (1974).
- PARRATT, J.R. & MACKENZIE, J.E. Possible mechanism of action of oxyfedrine as an anti-anginal drug *Brit. J. Clin. Pharmacol.*, 11 (1981).
- RAFTERY, E.B. & WHITTINGTON, J. Clinical experience with oxyfedrine in patients with angina pectoris *Herz*, 1, 358-365 (N6) (1982).
- SOWTON, G.E., BALCON, R., CROSS, D., FRICK, M.H. Measurement of the anginal threshold using atrial pacing *Cardiovasc. Res.*, 1, 301-307 (1967).
- WHITTINGTON, J. & RAFTERY, E.B. A controlled comparison of oxyfedrine, isosorbide dinitrate and placebo in the treatment of patients suffering attacks of angina pectoris *Br. J. Clin. Pharmacol.*, 10, 211-216 (1980a).

17. WHITTINGTON, J. & RAFTERY, E.B. Oxyfedrine and propranolol: a controlled trial in angina pectoris Br. J. Clin. Pharmacol., 10, 439-442 (1980b).

18. WILLIAMS, D.O., BASS, T.A., GERWITZ, H., MOST A.S. Adaptation to the stress of tachycardia in patients with coronary artery disease: insight into the mechanism of the warm-up phenomenon, Circulation, 71, 687-692 (1985).

