Br. J. clin. Pharmac. (1981), **12**, 229–233

THE COMBINATION OF NIFEDIPINE AND PROPRANOLOL IN THE MANAGEMENT OF PATIENTS WITH ANGINA PECTORIS

ANN C. TWEDDEL, J.M. BEATTIE, R.G. MURRAY & I. HUTTON

University Department of Medical Cardiology, Royal Infirmary, Glasgow, G4 0SF

1 A double-blind cross over study was carried out to assess the effects of the combination of nifedipine and propranolol in 25 patients with chronic stable angina pectoris at β-adrenoceptor blockade.

2 Efficacy was judged objectively by a standardized exercise protocol using a bicycle ergometer and subjectively by patient assessment of anginal attack rate.

3 The combination of nifedipine and propranolol was shown to be effective with an increase in exercise time to angina and an increase in physical work capacity expressed in terms of calculated maximal oxygen uptake (Vo_2 max). There was an associated reduction in anginal attack rate.

4 The synergistic effect was even more pronounced after reduction in propranolol dosage to 50% of the β-adrenoceptor blocking dose, reflecting the myocardial depressant effects of β-adrenoceptor blocking drugs in these patients with coronary heart disease, some of whom had poor left ventricular function.

Introduction

β-adrenergic receptor blocking agents have addded a new dimension to the medical management of patients with stable angina pectoris (Amsterdam, Gorlin & Wolfson, 1969; Hamer & Sowton, 1966; Gianelly *et al.*, 1967). However, unwanted and potentially hazardous side effects have been documented in as many as 10% of patients (Greenblatt & Koch-Weser, 1974). Further, in patients with impaired left ventricular function, β-adrenoceptor blockers may reduce exercise tolerance despite a reduced incidence of chest pain (Opie, 1980; Crawford *et al.*, 1975). There is therefore a potential role for an additional anti-anginal agent to permit a lower β-adrenoceptor blocking dose regimen. This may have the dual advantage of minimizing the risk of side-effects whilst enhancing physical work capacity.

Nifedipine, a calcium antagonist, which is both a coronary and peripheral vasodilator (Fleckenstein, Tritthart & Doring, 1972; Lydtin *et al.*, 1975) has proved a promising anti-anginal agent (De Ponti, Mauri, Ciliberto & Caru, 1979; Atterhog, Ekelund & Myelin, 1975), and a recent report has suggested that the combination with a β-adrenoceptor blocker is of potential value (Ekelund & Oro, 1979). This study was designed therefore to evaluate the anti-anginal efficacy of the addition of nifedipine to β-adrenoceptor blocker therapy in 25 patients with stable angina pectoris. A double-blind cross-over protocol was used with both a maximal β-adrenoceptor blocking dose and reduced β-adrenoceptor blocking dose regime.

Methods

Twenty-five patients were selected for study, 23 male and 2 female; mean age 52 years (range 39 to 59 years). Each had stable angina of more than 3 months' duration and reproducible exertional chest pain. Electrocardiographic criteria for entry to the study were either the evidence of a previous myocardial infarction on the resting ECG or a positive exercise test (ST depression $>$ 1 mm of duration 0.08 s). Fifteen patients had arteriographic confirmation of significant coronary disease (reduction of luminal diameter $>$ 50% in one or more of major coronary vessels). Patients with clinical congestive cardiac failure, hypertension (diastolic BP $>$ 100 mmHg) and chronic obstructive airways disease were excluded. All cardioactive drugs, except glyceryl trinitrin, were discontinued 1 week prior to the study.

The protocol is tabulated in Figure 1. Clinical examination was carried out at each visit and patients questioned for side-effects. Anginal frequency and glyceryl trinitrin consumption were recorded on diary cards. Exercise testing was performed using a bicycle ergometer. The ECG was monitored continuously using a modified V_5 electrode and blood pressure sampled intermittently by conventional sphygmomanometer during exercise and in the recovery period. A graded exercise protocol was used with an initial workload of 300 kpm (50 watts), increasing by 300 kpm at 3 min intervals until the onset of chest pain. An indirect estimate of maximal oxygen consumption (Vo_2 max) at peak exercise was obtained

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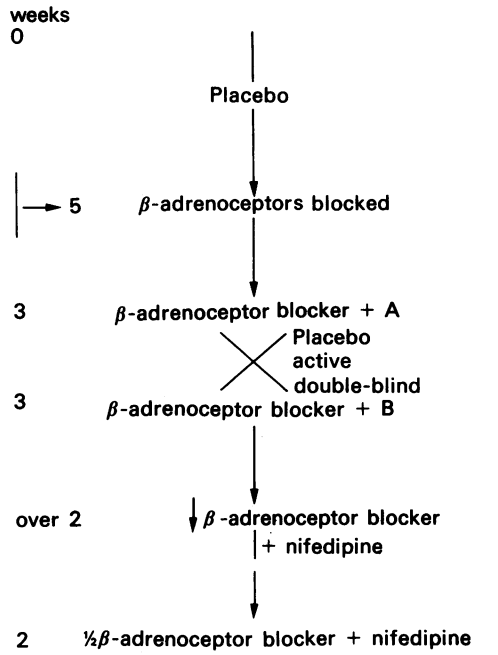

Figure 1 A diagram outlining the design of the study.

from the equation below (Blomqvist, 1973).

$$Vo_2max = \frac{(Workload \times 2) + 300\ ml\ kg^{-1}\ min^{-1}}{Body\ weight}$$

Workload = kpm at end point of exercise corrected for duration of exercise.

Body weight = kg

This was used as an index of physical work capacity.

After an initial placebo phase patients were commenced on propranolol, with increasing doses at weekly intervals until a resting heart rate of less than 60 beats/min was obtained, and there was a 30% reduction in exercise tachycardia. Patients were then randomly allocated to the addition of placebo or nifedipine in a dose of 10 mg, three times daily to their β-adrenoceptor blocking therapy in a double-blind cross-over fashion over two consecutive 3 week periods. Finally the β-adrenoceptor blocking dose of propranolol was gradually halved over a 2 week period. Patients continued on the 50% β-adrenoceptor blocking dose and nifedipine for a further 2 weeks, at which time a final exercise test and clinical assessment was made.

At each stage of the trial, blood samples were taken for haematological and biochemical screening. Patient compliance was assessed by measurement of plasma levels of nifedipine and propranolol.

Statistical analysis used was both parametric (Student's *t*-test) and non-parametric (Wilcoxon's Sign Rank Test).

Results

Eighteen of the 25 patients completed the study. Two patients died, one during escalation of the dosage of propranolol and the second having just started on nifedipine therapy. One patient suffered a myocardial infarction, one patient's anginal pattern became unstable, and there were three non-compliers.

Anginal frequency decreased from a mean of 10 ± 2 attacks per day during placebo therapy to 7 ± 2 per day when treated with propranolol, to 5 ± 2 attacks per day when nifedipine therapy was added ($P < 0.05$). This decrease in anginal attack rate was maintained when the dose of β-adrenoceptor blocker was halved, to 4 ± 2 daily episodes ($P < 0.05$). Similarly, there was a reduction in glyceryl trinitrin consumption from 11 ± 3 tablets per day on placebo to 7 ± 3 tablets daily on a combination of both drugs.

This subjective evidence was confirmed by objective data using symptom limited maximal exercise testing, the detailed results of which are found in Table 1. It can be seen that the exercise time was prolonged with propranolol and with the combination of nifedipine and propranolol. In addition the combination of nifedipine and 50% propranolol dosage significantly increased the exercise time when compared with propranolol alone ($P < 0.02$).

Table 1 The effects of dynamic exercise testing on physical work capacity

	Placebo	*Propranolol*	*Nifedipine + propranolol*	*Nifedipine + ½ propranolol*
Exercise time (min)	4.35 ± 0.4	4.8 ± 0.4	4.82 ± 0.5	5.06 ± 0.4**
Vo_2 max (ml kg^{-1} min^{-1})	16.16 ± 1.2	16.94 ± 1.3	17.8 ± 1.4	18.74 ± 1.2*
Vo^2 max (%)	55.08 ± 4.2	55.64 ± 4.4	59.98 ± 4.6	63.5 ± 3.9*

*$P < 0.05$, **$P < 0.02$

Results are mean ± s.e.mean of 18 patients.

Physical work capacity expressed in terms of calculated maximal oxygen consumption (Vo_2 max) was increased by nifedipine and propranolol from 16 ± 1 to 18 ± 1 ml kg^{-1} min^{-1} (Figure 2). In addition the

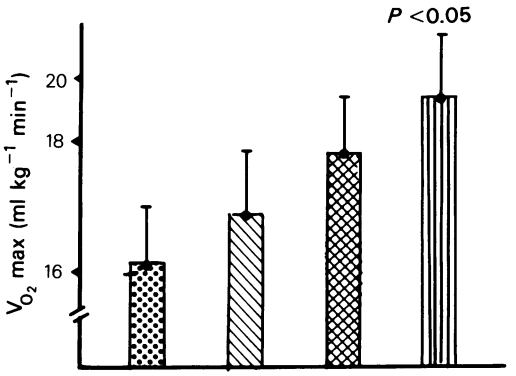

Figure 2 The effect of placebo (▨), propranolol (▧), nifedipine + propranolol (▩) and nifedipine + ½ propranolol (▥) on maximal oxygen consumption (Vo_2 max). Mean ± s.e.mean results ($n = 18$).

combination of nifedipine and 50% propranolol dosage significantly increased Vo_2 max when compared with propranolol alone ($P < 0.05$). If maximal oxygen capacity is expressed as a percentage of the expected normal for age and sex, a significant increase was produced by nifedipine and 50% propranolol from 55% ± 4 to 64% ± 4 ($P < 0.05$) (Figure 3).

Resting heart rate fell from a mean of 73 ± 3 beats/min on placebo to 50 ± 2 beats/min when patients were on propranolol. This rose slightly to 52 ± 2 beats/min with the addition of nifedipine, a further insignificant rise to 56 ± 2 beats/min when the propranolol dosage was reduced by 50%.

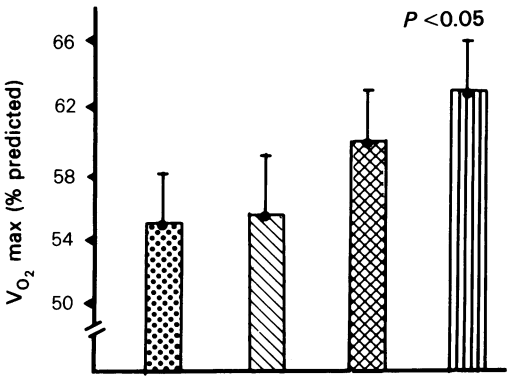

Figure 3 The effect of placebo (▨), propranolol (▧), nifedipine + propranolol (▩) and nifedipine + ½ propranolol (▥) on maximal oxygen consumption (Vo_2 max) expressed as % of the expected normal for age and sex. Mean ± s.e.mean results ($n = 18$).

Exercise tachycardia was significantly attenuated both by propranolol and the combination of propranolol and nifedipine (Table 2). There was no significant change in systolic or diastolic blood pressure at rest or on exercise.

Calculated double product ($HR \times SBP \times 10^{-3}$) was significantly reduced on propranolol from 19 ± 0.7 to 12 ± 0.7 ($P < 0.001$). This was maintained when nifedipine was added, but increased to 15 ± 1 when propranolol dosage was reduced.

Drug levels were used to assess patient compliance. Mean nifedipine level was 45 ± 63ng/ml and 39 ± 11 when the propranolol dose was halved. This demonstrates adequate serum levels of nifedipine (therapeutic level > 10 ng/ml). Similarly adequate plasma propranolol levels were obtained, mean propranolol being 133 ± 21 ng/ml. This level was slightly lower when nifedipine was added

Table 2 The effects of dynamic testing on paemodynamics

	Placebo		*Propranolol*		*Nifedipine + Propranolol*		*Nifedipine + ½ propranolol*	
	Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
Heart rate (beats/min)	73 ±3	118±4	50 ±2**	84 ±4**	52 ±2**	89 ±3**	56 ±2**	96 ±4**
Systolic BP (mmHg)	128 ±4	165±5	130 ±4	148 ±6	120 ±4	150 ±5	123 ±6	160 ±5
Diastolic BP (mmHg)	84 ±3	94±3	83 ±4	87 ±5	79 ±3	88 ±3	81 ±4	86 ±4
Heart rate × Systolic BP $\times 10^{-3}$	9.2±0.7	19±0.9	6.3±0.3	12.1±0.7**	6.3±0.3	13.4±0.7**	6.9±0.4	15.5±1*

*$P < 0.005$, **$P < 0.001$
Results are mean ± s.e.mean of 18 patients.

(99 ± 18 ng/ml), but still above that accepted as full β-adrenoceptor blockage (Coltart & Shand, 1970). Mean propranolol levels fell to 45 ± 9 ng/ml when propranolol dosage was reduced by 50%.

None of the patients reported adverse side effects related to nifedipine therapy in combination with propranolol and no abnormality was found on routine haematological and biochemical screening.

Discussion

The combination of nifedipine and propranolol is efficacious as an anti-anginal regime, as reflected by a decrease in anginal attack rate and glyceryl trinitrin consumption, an increase in time to angina, and physical work capacity expressed in terms of calculated V_{O_2} max and percentage V_{O_2} max. In addition nifedipine, in combination with a reduced propranolol dosage, is significantly better than propranolol alone as measure by an increase in exercise time and V_{O_2} max.

It is of interest that in this particular group of patients, some of whom had poor left ventricular function, that the improvement in both their time to angina and V_{O_2} max was modest on propranolol alone, but was significantly improved on the reduced dose of propranolol and nifedipine in particular. The probable explanation for this is the fact that eight of these patients had poor left ventricular function, with ejection fractions less than 40%.

Dynamic exercise testing provided an objective, qualitative evaluation of physical work capacity or maximal oxygen consumption (Mitchell & Blomqvist, 1971). Comparison of the patients' data with expected normal values of maximal oxygen uptake provide an objective assessment of the degree of impairment and thus an evaluation of therapeutic intervention.

The mechanism of action of nifedipine is not entirely clear, but it would appear to be a calcium antagonist which produces vasodilation by inhibiting smooth muscle contraction and acts preferentially on coronary, cutaneous and muscular arteries (Hempler & Proudfit, 1979), with little or no detrimental effect on myocardial muscle. Nifedipine has been shown in hypertensive patients to reduce systemic vascular incidence by 40% both acutely and after treatment for 29 days (Olivari *et al.*, 1979). In this study there appeared to be little or no influence on left ventricular filling pressure as measured by the pulmonary capillary wedge pressure. Similar results have been reported in patients with coronary heart disease by Dargie *et al.* (1980). The haemodynamic effects of nifedipine in the presence of β-adrenoceptor blockade have been assessed by Joshi *et al.* (1980), who found a reduction in systemic vascular resistance of 20% and a modest negative inotropic effect in these patients with coronary heart disease. Arteriolar vasodilatation has also been reported by Klugman, Salvi & Camerini (1980) in patients with congestive cardiac failure, resulting in improved left ventricular performance. This arteriolar vasodilating effect of nifedipine should result in a reduction in myocardial oxygen consumption (Braunwald, 1971). Thus the principal anti-anginal effect of nifedipine would appear to be a reduction in myocardial oxygen consumption related to arteriolar vasodilatation. The anti-anginal effects of β-adrenoceptor blockers and nifedipine would appear to be complementary with an overall reduction in myocardial oxygen consumption consequent to the reduction in heart rate and the negative inotropic effect exerted by propranolol and the peripheral effects of nifedipine. There are therefore theoretical advantages in combining nifedipine with a non-selective β-adrenoceptor blocker such as propranolol in the hope of reducing some of the side-effects attributed to β-adrenoceptor blockade. In this study, no side-effects were reported and there was good patient compliance.

An alternative method of assessing anti-anginal therapy is the use of exercise praecordial mapping (Fox, Selwyn & Shillingford, 1978). Using this technique Oakley *et al.* (1979) have demonstrated that the combination of nifedipine and propranolol was significantly better than the use of either drug alone in an open study of the treatment of patients with angina. In this study, with a relatively large number of patients, there would appear to be objective evidence for a synergistic effect between nifedipine and propranolol.

This study demonstrated that the combination of propranolol and nifedipine is safe and effective in the management of patients with stable angina. The combination of both drugs would appear to be more effective than propranolol alone, and the addition of nifedipine permits a reduced dosage of β-adrenoceptor blockade whilst patients are improved both subjectively and objectively.

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(Received September 11, 1980)