Use of exercise Doppler for non-invasive haemodynamic optimization of dose and identification of poor responders to an oral anti-anginal agent. A double-blind dose-finding study of nisoldipine

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Summary: Nisoldipine, a new dihydropyridine calcium antagonist, was examined for its dose-related haemodynamic effects using exercise-induced changes in aortic blood flow as measured by Doppler ultrasound. Following a two-week placebo run-in, 24 patients with stable angina pectoris were assigned double-blind to one of three groups receiving doses ranging from 2.5-20 mg/day over 8 weeks, given once or twice daily. Doppler studies identified the low dose group as responding less well at the placebo phase compared to the other two groups. There was an overall improvement in percentage change of peak velocity and stroke distance with exercise at all doses, with a dose of 5 mg/day giving optimal benefit in both variables ($P < 0.05$) and no additional benefit being seen on twice-daily dosage. Six patients reporting increased chest pain exhibited a significantly worse rise in peak velocity and a fall in stroke distance to exercise ($P < 0.05$) whilst on active drug compared to those who responded favourably. Doppler ultrasound can be of benefit in the haemodynamic assessment of new drugs, the recognition of non-responders and the optimization of therapeutic regimes.

Introduction

Nisoldipine, a dihydropyridine calcium antagonist structurally related to nifedipine, is a putative treatment for the prophylaxis of angina pectoris.¹⁻² This study was undertaken to investigate the effects of different dosages, given either once or twice daily, on left ventricular function using changes in aortic blood flow on exercise as measured by Doppler ultrasound. Any relationship between the degree of change and symptomatic response could also be assessed. Furthermore, exercise Doppler has been shown to be a sensitive method of identifying patients with significant heart disease³⁻⁵ and the effect of a potent anti-anginal agent on these measured variables would be seen.

Materials and methods

Patients with a typical history of stable angina pectoris were sought and informed consent was

obtained prior to entry. Exclusions were heart failure; significant valvular disease; high degree atrio-ventricular block, bradycardia or tachyarrhythmias; females capable of child-bearing; those with significant hepatic, renal or gastro-intestinal disease; known intolerance to calcium antagonists; and unstable angina.

All anti-anginal medication other than glyceryl trinitrate was discontinued. After a 2-week placebo (1 tablet twice daily) run-in period, patients were randomly allocated double-blind to receive nisoldipine 2.5 mg, 5 mg or 10 mg. This was initially taken every morning for 4 weeks with matching placebo in the evening, and then twice daily for a further 4 weeks.

Severity and frequency of angina were assessed by daily diary cards kept by the patient, from fortnightly interviews and from counts of glyceryl trinitrate tablets returned. Compliance was measured by fortnightly tablet counts.

On entry and at the end of each treatment phase (weeks 0, 2, 6, 10) patients were exercised on a cycle ergometer (Borsch ERG 555) while positioned semi-erect on a couch. A minimum of 2 hours elapsed between glyceryl trinitrate ingestion and exercise

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testing. Patients were required to maintain a constant speed of 50 rev/min and the workload increased automatically by 10 watts every minute. Exercise was terminated by angina, dyspnoea, fatigue or leg pains.

Blood pressure (BP), using a standard sphygmomanometer, and heart rate were recorded under baseline conditions immediately before exercise following a minimum of 3 minutes' rest, at 3-minute intervals during exercise and, finally, at completion.

Doppler recordings of aortic blood velocity were made after a minimum of 3 minutes' rest and at peak exercise using a Spectrascan Analyser (Doptek Ltd., Chichester, Sussex, UK). Continuous wave 2 MHz Doppler ultrasound was used via a supra-sternal approach with the transducer aimed at the ascending aorta. Optimization of the received signal was achieved using pitch heard through a loud-speaker and visual inspection of the velocity waveform produced by spectral analysis. Aortic blood peak velocity (PV) was measured from the Doppler recordings; stroke distance (SD) was obtained by integration of the area under the velocity-time waveform envelope and minute distance (MD), a value analogous to cardiac output, calculated as the product of SD and heart rate^{6,7} (Figure 1).

Figure 1 Doppler recordings at rest and exercise.

A minimum of 5 beats was averaged for the calculation of stroke distance and peak velocity. These beats were consecutive where possible; however, breathing artefact did not allow this in the majority of exercise recordings. To compensate for beat-to-beat changes in respiration and transducer movement any measurement less than 75% of the maximum obtained was disregarded for calculation purposes.

An index of systemic vascular resistance was measured as:

$$\frac{\text{diastolic BP} + 0.33 (\text{systolic} - \text{diastolic BP})}{\text{minute distance}} \times 80$$

Statistical analysis was performed using analysis of variance, Wilcoxon rank sum and 2-sample tests and Student's *t*-test.

The study was approved by the Hillingdon District Ethical Committee.

Results

Twenty-four patients were studied, 8 in each treatment group. Patient details are shown in Table I.

Adverse events were reported by 10 patients, leading to the withdrawal of 6 of them, and are shown in Table II. A total of 6 patients complained of increasing severity or frequency of chest pain.

Table I Group characteristics

	2.5 mg group		5.0 mg group		10.0 mg group	
Sex	1 f	7 m	5 f	3 m	2 f	6 m
Age (y) (mean ± s.d.) (range)	(57–82)		(56–70)		(45–83)	
Previous myocardial infarction	2		1		2	
Median duration of angina (range)	4 y (0.35–7.9)		1.2 y (0.35–4.0)		0.5 y (0.25–1.75)	

Table II Unwanted effects and withdrawals

	2.5 mg	5 mg	10 mg
Chest pain	2(1)	2(2)	2(1)
Oedema	1	1(1)	1
Headache, flushing		1(1)	1

Figures in parentheses indicate withdrawals.

Subjective improvement

During the 14-day placebo phase there was no significant difference in angina frequency between the three treatment groups, the median number of days in which angina was reported being 8, 6.6 and 12 days for those allocated to 2.5 mg, 5 mg and 10 mg nisoldipine, respectively.

After the once-daily phase there was a reduction in frequency of angina, more so for those on 5 mg and 10 mg groups respectively (Figure 2). Although daily phase all 3 treatment groups showed improvement in symptoms compared with placebo, the median number of days with angina in the final fortnight being 2, 3 and 5 days for the 2.5 mg, 5 mg and 10 mg groups respectively. (Figure 2) Although these reductions were not significant, a trend is, however, apparent.

Exercise testing

An increase in exercise duration was noted with all doses and through both once- and twice-daily phases with significant increases at the twice-daily phase of each dose ($P < 0.05$) (Table III).

All three groups showed non-significant decreases in resting blood pressure, more so at the twice-daily

dosage, with average falls of 5–8.5%. With exercise there were similar percentage increases in systolic and diastolic blood pressure for each treatment group at both once- and twice-daily phases compared with placebo. There were no significant changes in heart rate at any dose level compared with placebo, either at rest or at maximal exercise.

Exercise Doppler

Satisfactory recordings were achieved on all patients before and at peak exercise. Difficulty in insonation of the aorta was experienced in 1 patient in the 10 mg group at week 10 on peak exercise. This resulted in a delay of 30–40 seconds and, as a consequence, his measured minute distance (MD) would be lower and stroke distance (SD) higher than might have been the case at peak exercise.

There was no significant difference in resting values of stroke distance, peak velocity (PV), minute distance and heart rate between dosage groups, or between placebo, once- and twice-daily phases.

On exercise there was no significant difference in % increase in heart rate, either between groups or phases. Percentage change in PV, SD and MD with exercise increased after the once-daily phase, with no significant further improvement on twice-daily dosage. This difference was most marked with those in the 5 mg group (Figure 3). The fall in systemic vascular resistance (SVR) with exercise was greater than placebo values in all three treatment groups though did not reach statistical significance.

Of the 6 patients complaining of increased chest pain 4 were exercised after commencement of active drug. Two of these patients had noted little change in angina symptoms but subsequently withdrew during the twice-daily dosage phase following a single severe episode of chest pain, one being a proven myocardial infarction. At the placebo phase the percentage change in PV and SD on exercise in these 4 patients was not significantly different to that shown by the other 17 subjects who were also able to exercise at least once on active drug. At the end of the once-daily treatment phase there was a significantly poorer response in both Doppler variables in those with increased chest pain compared to the others ($P < 0.05$). Whilst patients responding to the drug showed a marked improvement ($P < 0.01$ for % change PV, $P < 0.05$ for % change SD), those with increased chest pain exhibited a non-significant deterioration (Figure 4).

Correlation was also found ($P < 0.05$) between the degree of improvement in both % change SD and MD and subjective improvement in symptoms at the once-daily phase, irrespective of dose. No inter-group differences were noted.

Figure 2 Fortnightly frequency of angina (median $\pm$ s.e.m.). O.D. = once daily; B.D. = twice daily.

Table III Exercise test duration (mean $\pm$ s.e.m.)

Dose (mg)	Total exercise duration (min)		
	2.5	5.0	10.0
Placebo	6.3 $\pm$ 2.5	6.3 $\pm$ 2.7	6.2 $\pm$ 3.0
Once a day	7.1 $\pm$ 2.2	7.4 $\pm$ 2.3	6.9 $\pm$ 2.5
Twice a day	7.5 $\pm$ 3.0*	8.0 $\pm$ 2.0*	8.1 $\pm$ 2.6*

* $P < 0.05$.

Figure 3 Percentage change with exercise in stroke distance (SD), minute distance (MD), peak velocity (PV) and systemic vascular resistance (SVR) (mean $\pm$ s.e.m.).

Discussion

The majority of subjects tested in this study showed a beneficial response to nisoldipine in both symptoms and haemodynamic response as measured by changes in Doppler variables on exercise. A daily dose of 5–10 mg nisoldipine/day appeared to provide optimal benefit. No further change was noted in the haemodynamic response to a twice-daily dosage regime in all groups. No added symptomatic benefit was seen in the 5 mg and 10 mg groups on twice-daily dosage although the once-daily dose of 2.5 mg appeared to have little effect on the frequency of angina attacks. Six patients complained of increased severity or frequency of chest pain; 4 of these were exercised whilst on active drug and showed no significant change in either blood pressure or heart rate but did exhibit a significantly worse haemodynamic response to exercise compared with the other subjects.

Exercise Doppler has been shown to be a sensitive means of identifying patients with ischaemic heart disease.^{3–5} Allowing for variation due to differing techniques and exercise protocols, a diminished exercise response in peak velocity and stroke distance is seen in patients with ventricular dysfunction.

Values obtained in our laboratory for normal subjects ($n=10$, mean age 49.8 ± 5.8 years, range 42–60) using the same exercise protocol and equipment revealed an average rise on exercise of $38 \pm 6\%$ in peak velocity and a virtually unchanged stroke distance (-3%). Reproducibility of exercise Doppler findings in these patients was 12% (Singer & Trotman submitted for publication). This compares with an overall fall of $-0.8 \pm 6\%$ in peak velocity ($P < 0.001$) and $-9.6 \pm 5\%$ in stroke distance ($P < 0.05$) on exercise at the placebo phase of this study in patients with angina pectoris. There was, however, no significant difference in Doppler variables between ischaemic heart disease and control groups measured at rest. Thus the addition of stress in the form of semi-erect exercise enabled differentiation.

This study is the first reported in which Doppler ultrasound has been used to systematically evaluate on a double-blind basis the haemodynamic dose effects of an orally cardio-active drug. Changes in peak velocity provide a good indication of myocardial performance.^{8–9} In those patients who responded favourably to nisoldipine, peak velocity and stroke distance did increase further with exercise when on active drug (overall to $+17 \pm 6\%$ and

Figure 4 Comparison of exercise Doppler response in those showing a beneficial response and those complaining of increased chest pain.

$-1 \pm 3\%$) and there was a non-significant reduction in systemic vascular resistance. Nisoldipine has been shown to be 4–10 times more potent than nifedipine in the inhibition of vascular smooth muscle contraction with less myocardial depressant

effects.¹⁰ Thus the improvement in left ventricular performance as reflected by changes in Doppler variables on exercise may well be due to a combination of improved myocardial perfusion from coronary artery vasodilatation with afterload reduction by its peripheral actions. In those whose symptoms worsened there was no such improvement. Whether this can be attributed to the drug is open to conjecture; previous reported studies have reported only isolated unwanted effects^{1,11} and further evaluation is obviously warranted.

The improvement seen in the Doppler variables on nisoldipine in those who had a beneficial response resulted in no significant difference being seen in stroke distance on exercise between this ischaemic heart disease group and the group of normals previously tested. Statistical significance was however still noted in the peak velocity response to exercise ($P < 0.001$) which appears to be a more sensitive parameter. This finding indicates that the maximum sensitivity of the technique in diagnosing left ventricular dysfunction is in the absence of cardio-active drugs and further studies are necessary to assess the effect of beta-blockers and so forth.

The degree of improvement in Doppler-measured variables on exercise was shown to correlate with subjective improvement in symptoms; it further appeared to be a highly sensitive indicator of individual deterioration as, of the 6 poor responders, 3 withdrew due to chest pain and 1 noted increasing frequency of angina.

The technique may therefore be used not only for the assessment of new drugs where more invasive methods are either impossible or inappropriate but also to haemodynamically optimize therapeutic regimes and identify negative responders.

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References

1. Lopez, L.M., Rubin, M.R., Holland, J.P. & Mehta, J.L. Improvement in exercise performance with nisoldipine, a new second-generation calcium blocker, in stable angina pectoris. *Am Heart J* 1985, **110**: 991–996.
2. Lam, J., Chaitman, B.R., Crean, P., Blum, R. & Waters, D.D. A dose-ranging, placebo-controlled, double-blind trial of nisoldipine in effort angina: duration and extent of antianginal effects. *J Am Coll Cardiol* 1985, **6**: 447–452.
3. Mehta, N. & Bennett, E.D. Impaired left ventricular function in acute myocardial infarction assessed by Doppler measurement of ascending aortic blood velocity and maximum acceleration. *Am J Cardiol* 1986, **57**: 1052–1058.
4. Bryg, R.J., Labovitz, A.J., Mehdirdad, A.A., Williams, G.A. & Chaitman, B.R. Effect of coronary artery disease on Doppler-derived parameters of aortic flow during upright exercise. *Am J Cardiol* 1986, **58**: 14–19.

5. Teague, S.M., Mark, D.B., Radford, M. *et al.* Doppler velocity profiles reveal ischemic exercise responses (abstr). *Circulation* 1984, **70** (suppl II): 185.
6. Light, L.H. & Cross, G. Convenient monitoring of cardiac output and global left ventricular function by transcutaneous aortovelocity— an effective alternative to cardiac output measurements. In: Spencer, M.P. (ed) *Cardiac Doppler Diagnosis*. Martinus Nyhoff, The Hague, 1983, pp 69–82.
7. Huntsman, L.L., Stewart, D.K., Barnes, S.R., Franklin, S.B., Colocousis, J.S. & Hessel, E.A. Noninvasive Doppler determination of cardiac output in man. Clinical validation. *Circulation* 1983, **67**: 593–602.
8. Distante, A., Moscarelli, E., Rovai, D. & L'Abbate, A. Monitoring of changes in cardiac output by transcutaneous aortovelocity, a non-invasive Doppler technique: comparison with thermodilution. *J Nucl Med All Sci* 1980, **24**: 171–175.
9. Bennett, E.D., Barclay, S.A., Davis, A.L., Mannering, D. & Mehta, N. Ascending aortic blood velocity and acceleration using Doppler ultrasound in the assessment of left ventricular function. *Cardiovasc Res* 1984, **18**: 632–638.
10. Kazda, S., Garthoff, B., Meyer, H. *et al.* Pharmacology of a new calcium antagonist compound, isobutyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (nisoldipine, Bay k 5552). *Arzneimittelforsch (Drug Res)* 1980, **30**: 2144–2162.
11. Silke, B., Fraiss, M.A., Muller, P., Verma, S.P., Reynolds, G. & Taylor, S.H. Haemodynamic dose-response effects of intravenous nisoldipine in coronary artery disease. *Br J Clin Pharmacol* 1985, **20**: 675–680.