Effects of dilevalol (R,R-labetalol) compared with nifedipine on heart rate, blood pressure and muscle blood flow at rest and on exercise in hypertensive patients

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- 1 Dilevalol (R,R-labetalol) is a non-selective β -adrenoceptor antagonist with β_2 -adrenoceptor agonist activity. Its effects after 1 month's administration on heart rate, blood pressure and muscle blood flow were studied in a double-blind crossover comparison with nifedipine in 16 hypertensive patients.
- 2 Dilevalol and nifedipine were similarly effective in lowering systolic and diastolic blood pressure at rest, but dilevalol limited the rise in systolic blood pressure induced by exercise more than nifedipine (rise of 27 vs 53 mm Hg respectively, $P < 0.01$).
- 3 Dilevalol decreased resting heart rate compared with nifedipine (73 vs 92 beats min^{-1} respectively, $P < 0.01$). Dilevalol limited the exercise induced rise in heart rate more than nifedipine (36 vs 48 beats min^{-1} respectively, $P < 0.01$).
- 4 Muscle blood flow (measured by strain gauge plethysmography) was not affected by either dilevalol or nifedipine at rest. After exercise, dilevalol caused an increase in excess blood flow compared with placebo (10.8 vs 5.1 $\text{ml min}^{-1} \text{dl}^{-1}$ respectively, $P < 0.01$). The difference between dilevalol and nifedipine did not reach statistical significance (10.8 vs 6.5 $\text{ml min}^{-1} \text{dl}^{-1}$ respectively, $P > 0.05$).
- 5 On blood pressure and heart rate, dilevalol demonstrated β -adrenoceptor blocker activity at rest and on exercise. On muscle blood flow, dilevalol appeared to have no effect at rest, but may have acted as a β -adrenoceptor blocker rather than as a β_2 -adrenoceptor agonist during exercise.

Keywords dilevalol nifedipine pharmacodynamics hypertension exercise

Introduction

Dilevalol is the R,R-isomer of labetalol, and is a non-selective β -adrenoceptor antagonist with β_2 -adrenoceptor agonist activity (Chrisp & Goa, 1990). It has three to six times the activity of labetalol at the β -receptor, but unlike labetalol, little activity at the α_1 -receptor (Sybertz *et al.*, 1981). In animal studies, it causes vasodilation even in denervated limbs (unlike α -adrenoceptor blockers such as prazosin), which is blocked by propranolol, suggesting that these vasodilator effects are due to β_2 -adrenoceptor agonism (Baum *et al.*, 1981). It lowers blood pressure, both in normal (Fujimara *et al.*, 1984, 1989; Lambeth *et al.*, 1989; MacLennan *et al.*, 1989) and hypertensive subjects (Bugni *et al.*, 1989; Strom *et al.*, 1989). Because the fall in blood pressure correlates with a fall in peripheral vascular resistance rather than a decrease in cardiac index (in contrast to atenolol or metoprolol), it is

thought to be due to the β_2 -adrenoceptor agonist induced vasodilation, rather than to non-specific β -adrenoceptor antagonist effects (Strom *et al.*, 1989). In comparative studies with other β -adrenoceptor blockers, dilevalol is as effective in hypertension as propranolol, with fewer adverse effects (Schoenberger *et al.*, 1989) and similar to atenolol and metoprolol (Strom *et al.*, 1989).

In the treatment of hypertension, β -adrenoceptor blockers may cause fatigue, particularly during exercise. This is partly centrally mediated, and partly due to diminished muscle blood flow in turn caused by decreased cardiac output and by antagonism of vasodilator β_2 -adrenoceptors in the arterial vessels to large muscles. Vasodilators avoid this, but are less effective in attenuating any exercise induced rise in heart rate or blood pressure. Dilevalol might maintain muscle blood flow,

while decreasing exercise induced tachycardia and rises in blood pressure. To study this, a comparison of the haemodynamic effects of dilevalol and the calcium channel blocker nifedipine was undertaken at rest and on exercise in hypertensive patients.

Methods

Study design

A double-blind crossover (in random order, by blocks of four) comparison of dilevalol and nifedipine was performed. Patients were given placebo for 2 weeks followed by active therapy for 4 weeks and then given the alternate therapy for a further 4 weeks. Assessments were performed at the end of each treatment phase.

Inclusion and exclusion criteria

Patients aged 18–70 years with mild to moderate hypertension (diastolic 95–109 mm Hg, systolic < 210 mm Hg), and who were either previously untreated or had discontinued antihypertensive drugs (for clinical reasons) for at least 8 weeks were eligible for inclusion in the trial. Patients with contraindications to or histories of previous adverse effects to β -adrenoceptor blockers or nifedipine, secondary hypertension, known ischaemic heart disease or cerebrovascular disease or peripheral vascular disease, or women of child bearing age were excluded.

Patients were examined on three occasions over 4 weeks and hypertension confirmed before entering the placebo run in phase.

Assessments

Assessments were carried out at the same time of day for each patient, 2 h after the morning medication.

1. Blood pressure (Korotkoff phase V) was measured with a Hawksley random zero sphygmomanometer, after 5 min supine rest and after 2 min standing (mean of two readings for each). During exercise, blood pressure was measured using a standard sphygmomanometer. Systolic and diastolic pressure were recorded each time and also the rise in blood pressure (above lying pressures) during peak exercise.

An interim measurement of blood pressure was made after 2 weeks of active treatment for dose titration purposes (see below) and again for the main comparison of the effects of the two drugs, at the end of each treatment phase.

2. Heart rate was measured by counting at the radial pulse for 30 s lying and standing (mean of two readings). During exercise, heart rate was read from a 10 s ECG print out, and the rise above lying heart rate recorded.
3. Muscle blood flow ($\text{ml min}^{-1} \text{dl}^{-1}$) was measured in the right calf using venous occlusion strain gauge plethysmography (Roberts *et al.*, 1986). The study room was air conditioned to a constant 23° C at all times. Blood flow (mean of four readings) was measured after 20 min supine rest and at 1 min intervals for 12 min immediately after exercise.

Figure 1 Total excess blood flow is the area under the blood flow curve from 2 to 12 min, minus the background resting flow. □ CBF after exercise, + background CBF, □ resting CBF.

Resting calf blood flow, peak blood flow after exercise, difference between resting and peak was recorded. The blood flow after exercise usually increased for a period after exercise: this is a reactive hyperaemia, the extent of which is an indication of the blood flow 'debt' incurred during the exercise and would be expected to be increased after a β_2 -adrenoceptor antagonist but decreased after vasodilators. The increase was measured by the area under the curve of the blood flow readings (by trapezoidal rule) less the basal flow, and is termed total excess blood flow (see Figure 1) (Roberts, 1990).

Exercise protocol

Exercise was performed on a fixed cycle ergometer (Tunturi) for 4 min at a workload set for each individual patient. During the placebo run in phase, patients performed two or more exercise tests for familiarisation, and to allow adjustment of the workload so that a target heart rate (85% of maximum by age for each patient) was achieved consistently by the end of the exercise period. Once established, the same workload was used for the assessment tests at the end of each trial phase. Electrocardiogram was monitored throughout the exercise test and blood pressure was measured at minute intervals.

Drugs and doses

Patients received matching placebo capsules during a 2 week run in phase, and then were given active therapy. The initial doses, known to be effective in hypertension (Garruti & Arnold, 1989; Glover & Tarbit, 1990; Schoenberger *et al.*, 1989; Vaccarella *et al.*, 1989), were dilevalol 200 mg day^{-1} (in the morning) or nifedipine (Adalat Retard) 10 mg twice daily, given in identical gelatin capsules with dummies as necessary to preserve study blinding. If the diastolic blood pressure was not

controlled after 2 weeks of active treatment (defined as < 90 mm Hg, or fallen by 10 mm Hg, whichever was lower), the doses could be doubled to 400 mg day⁻¹ or 20 mg twice daily respectively. Capsule counts were carried out to check compliance. Patients were asked to report all new symptoms for consideration as adverse effects.

Ethical considerations

The trial was approved by the local ethics committee. Patients gave written consent to participate after full explanation of the aims and procedures of the trial.

Statistical analysis

The primary comparison was between the haemodynamic effects of dilevalol and nifedipine, and results were analysed by the Hills Armitage procedure for crossover analysis with 2 sample *t*-test to test for treatment effect and for treatment by period interaction. The level of significance was taken to be 5%.

As a secondary analysis, the effects of dilevalol and nifedipine were compared with placebo by paired *t*-test: because of repeated testing, the level for significance for these tests was set at 1%. Results are shown as mean (s.d.).

The minimum statistically detectable difference for a probability of 0.05 and a power of 0.80 was calculated for each parameter measured, i.e. the smallest difference between treatments that was likely to be detected as significant given the number of patients and variations within and between patients (Pocock, 1984).

Results

Patients

Twenty-two patients entered onto the placebo phase. Blood pressure settled in two on placebo, and 20 patients (mean age 52 s.d. 8 years, 13 male, 7 female) entered the randomised phases of the trial. Drug compliance was over 90% at all phases by capsule count. There were four subsequent dropouts from active treatment: one patient

defaulted (on contact with his general practitioner, this was not due to adverse effects) and three patients suffered adverse effects requiring withdrawal from the trial: one because of severe heartburn (nifedipine), and two for severe fatigue (one nifedipine, one dilevalol). These four patients could not be included in the crossover analysis and results are therefore reported for the sixteen who completed both phases.

Other minor adverse effects reported during one or more active treatment phases, but not requiring drug withdrawal, were fatigue (four dilevalol, two nifedipine), dyspepsia (two nifedipine), and ankle oedema (two nifedipine).

Order effects

Nine patients received active drug in the order dilevalol/nifedipine and seven in the order nifedipine/dilevalol. There were no treatment by order interactions.

Blood pressure

Mean blood pressure before treatment was 168 (15)/104 (5) mm Hg. Ten patients were titrated to the higher dose of dilevalol and 12 for nifedipine, of a total of 32 treatment periods. Target blood pressure was achieved in eight patients on each drug. Systolic and diastolic blood pressures (lying and standing) are shown in Table 1, and response to exercise of systolic and diastolic blood pressure in Figure 2a and 2b. Both drugs lowered systolic and diastolic blood pressures to a similar degree, compared with the placebo phase. Dilevalol was more effective at limiting the rise in systolic blood pressure seen with exercise, while both drugs were similarly effective in limiting diastolic.

There was no significant postural fall in blood pressure.

Heart rate

Dilevalol lowered lying and standing heart rate and the rise in heart rate on exercise significantly compared with placebo and with nifedipine. Nifedipine increased standing heart rate significantly, but lowered the exercise induced increase in heart rate, compared with placebo (Table 1 and Figure 2c).

Table 1 Haemodynamic results. SBP systolic and DBP diastolic blood pressure; HR heart rate; CBF calf blood flow (***P* < 0.001 dilevalol or nifedipine vs placebo). Results are shown as mean (s.d.)

	Placebo	Dilevalol	Nifedipine	Dilevalol vs nifedipine
Lying SBP (mm Hg)	168 (15)	151 (23)**	153 (20)**	NS
Standing SBP (mm Hg)	170 (20)	147 (21)**	149 (15)**	NS
Lying DBP (mm Hg)	104 (5)	92 (9)**	89 (7)**	NS
Standing DBP (mm Hg)	105 (6)	95 (9)**	97 (11)**	NS
Lying HR (beats min ⁻¹)	82 (9)	68 (9)**	79 (10)	<i>P</i> < 0.01
Standing HR (beats min ⁻¹)	84 (8)	73 (8)**	92 (13)**	<i>P</i> < 0.001
Rest CBF (ml min ⁻¹ dl ⁻¹)	4.2 (1.6)	4.1 (1.7)	4.4 (1.9)	NS
Peak CBF (ml min ⁻¹ dl ⁻¹)	5.5 (2.5)	5.5 (2.1)	5.6 (2.5)	NS

Figure 2 Pharmacodynamic changes after exercise on placebo (■), dilevalol (▨) and nifedipine (▩). a) Mean change in systolic blood pressure on exercise. b) Mean change in diastolic blood pressure on exercise. c) Mean change in heart rate on exercise (mean and s.d.).

Figure 3 Mean change in excess calf blood flow after exercise on placebo (■), dilevalol (▨) and nifedipine (▩) (mean and s.d.).

Calf blood flow

There were no significant differences in calf blood flow at rest, at its peak after exercise or in the rise in calf blood flow after exercise. Total excess blood flow increased significantly on dilevalol compared with placebo (Figure 3). No changes were seen on nifedipine.

Detectable differences

The minimum detectable differences for the significance level and power desired and the size of the trial are shown in Table 2.

Table 2 Minimum statistical significant difference detectable given the number of subjects (16), significance level (5%), power desired (0.80) and variability seen for each measurement

Standing SBP (mm Hg)	13
Lying SBP	16
Change in SBP on exercise	15
Standing DBP	7
Lying DBP	6
Change in DBP on exercise	12
Standing HR (beats min ⁻¹)	6
Lying HR	6
Change in HR on exercise	11
Resting CBF (ml min ⁻¹ dl ⁻¹)	1.3
Peak CBF	1.7
Change in CBF after exercise	1.3
Total excess blood flow	10.8

Discussion

Both drugs reduced blood pressure to a similar degree, while dilevalol reduced exercise related systolic hypertension and heart rate. Dilevalol has previously been shown to be an effective antihypertensive agent in many studies, reaching its full antihypertensive effect within 2 weeks and maintaining it for at least 1 year (Baba *et al.*, 1988; Bugni *et al.*, 1989; Glover & Tarbit, 1990; Schoenberger *et al.*, 1989; Strom *et al.*, 1989). It is also effective in treating isolated systolic hypertension in the elderly (Silagy *et al.*, 1990). Although its antihypertensive effect at rest is thought to be due to vasodilation, the blunting of exercise induced heart rate and blood pressure rises is similar to the effects of classic β -adrenoceptor blockers. Increase in cardiac index on exercise is also limited by dilevalol (Bugni *et al.*, 1989; Lund Johanson, 1988). These results suggest that during exercise, the partial β_2 -adrenoceptor agonist activity is overcome by the β -adrenoceptor blocking effects.

The same may be true of muscle blood flow. At rest, dilevalol caused no reduction in calf blood flow despite a fall in blood pressure, clearly indicating a reduction in

peripheral resistance, in contrast to our earlier work with atenolol, pindolol and labetalol (Roberts *et al.*, 1987). Although cardiac output was not measured as part of this study, the fall in heart rate suggests that it was also reduced, and the lack of a reflex rise in peripheral resistance, as is usually seen with other β -adrenoceptor blockers, is still more marked. However on exercise, although the peak calf blood flow and the rise in calf blood flow were similar on either active drug or on placebo, the total excess blood flow was increased by dilevalol ($P < 0.001$, compared with placebo). This may suggest that there was a greater anoxic burden to be repaid after exercise on dilevalol, and perhaps that despite the β_2 -adrenoceptor agonist effects, muscle blood flow during exercise had been decreased, either by a fall in cardiac output or by pharmacological antagonism of the β -receptor in the blood vessels supplying the muscle, i.e. that on exercise again the β -adrenoceptor blocking effects of dilevalol predominate. This cannot be taken as a definite conclusion, since it is not derived from the primary analysis, i.e. comparison of dilevalol and nifedipine. The failure to detect a significant difference between the effects of dilevalol and nifedipine on total excess blood flow must be attributed to the power of the study; the variability seen was greater than that previously found in similar subjects (Roberts, 1990). Given the size of the difference and variability in this measurement, here, and the number of subjects involved, the power to detect the difference as significant can be calculated as only 0.20.

In comparisons with nifedipine, dilevalol was similar in antihypertensive efficacy but was better tolerated (Edwards, 1988; Garruti & Arnold, 1989; Vaccarella *et al.*, 1989). Dilevalol also seemed slightly better tolerated than nifedipine in the study reported here, but the numbers of patients involved preclude any further comparison.

There has been considerable interest in the possible advantages of enantiomers (such as dilevalol) over racemates (such as labetalol), in terms of less complex

pharmacology and possible reduction in adverse effects (Lennard, 1991). Although dilevalol has potential clinical advantages over labetalol, it was withdrawn worldwide in 1990 (before marketing in the UK), when there were a number of reports of associated hepatitis in Portugal and Japan where it was first launched. Three similar cases associated with labetalol were subsequently reported from the United States (Clark *et al.*, 1990). However the incidence of hepatitis associated with dilevalol was considerably greater than with labetalol, necessitating its withdrawal (D. Glover, personal communication). The mechanism of the hepatitis is unknown, and it is speculated that the racemate labetalol in some way protects against the toxicity of the enantiomer dilevalol (Lennard, 1991). Clearly, single enantiomers may not always be best option for clinical use and it cannot be assumed that they will have less toxicity than the racemate.

Some commentators have suggested that dilevalol reversed the fundamental defect in hypertension, i.e. increased vascular resistance while maintaining cardiac output at rest (Chrisp & Goa, 1990), and that a drug such as dilevalol represented a more physiological approach to the treatment of hypertension than standard β -adrenoceptor blockers (Waller, 1990). Although development of dilevalol itself has been terminated, β_2 -adrenoceptor partial agonism with non-specific β -antagonism or specific β_1 -adrenoceptor antagonism has been developed in a number of other compounds; celiprolol has already been marketed in the UK, and others will follow. From the present study, it seems that the behaviour of dilevalol at rest, where it is predominantly a vasodilator, and on exercise, where it seems predominantly a non-specific β -adrenoceptor blocker, are quite different. Whether combining these features in the one molecule represents a genuine therapeutic advance is uncertain at present (Editorial, 1991; Waller, 1990).

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References

- Baba, T., Murabayashi, S., Aoyagi, K. & Ishizaki, T. (1988). Effects of dilevalol, an R,R-isomer of labetalol, on blood pressure and renal function in patients with mild to moderate essential hypertension. *Eur. J. clin. Pharmac.*, **35**, 9–15.
- Baum, T., Watkins, R. W., Sybertz, E. J. *et al.* (1981). Anti-hypertensive and hemodynamic properties of SCH 19927, the R,R isomer of labetalol. *J. Pharmac. exp. Ther.*, **218**, 444–452.
- Bugni, W. J., Ayers, C. W., Ashby, R., Bittle, P. A. & Ramirez, G. (1989). Effects of dilevalol on rest and supine haemodynamics in mild to moderate systemic hypertension. *Am. J. Cardiol.*, **63**, 452–456.
- Chrisp, P. & Goa, K. (1990). Dilevalol; a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in hypertension. *Drugs*, **39**, 234–263.
- Clark, J. A., Zimmerman, H. J. & Tanner, L. A. (1990). Labetalol hepatotoxicity. *Ann. Intern. Med.*, **113**, 210–213.
- Editorial (1991). Celiprolol; theory and practice. *Lancet*, **338**, 1426–1427.
- Edwards, L. (1988). Action of a betablocking vasodilator compared to captopril, enalapril and nifedipine. Abstract, Symposium *Antihypertensive therapy in the 90s—the role of balanced haemodynamics* (reported in Chrisp & Goa, 1990).
- Fujimara, A., Ohashi, K., Tsuru, M., Ebihara, A. & Kondo, K. (1984). Clinical pharmacology of an α, β blocking agent, SCH 19927: repeated administration study in normotensive healthy volunteers. *Jap. J. Pharmac.*, **36** (suppl.), 98P.
- Fujimara, A., Ohashi, K., Tsuru, M., Ebihara, A. & Kondo, K. (1989). Clinical pharmacology of dilevalol (II). The pharmacokinetic, pharmacodynamic and tolerance studies of dilevalol during repeated administration in healthy subjects. *J. clin. Pharmac.*, **29**, 643–649.
- Garruti, R. J. & Arnold, G. (1989). Dilevalol, a new β blocking vasodilator, compared to enalapril and nifedipine in mild and moderate hypertension. In *Beta₂ partial agonism in the treatment of hypertension; results with dilevalol*. Satellite to the Fourth European meeting on hypertension, pp. 24–25. Macclesfield: Adelphi Communication.
- Glover, D. R. & Tarbit, W. (1990). Overview of clinical trials

- of dilevalol in essential hypertension. *J. Human Hypertension*, **4** (Suppl. 2), 49–53.
- Lambeth, M. A., Barnes, R. W., Given, B. D. & Affrime, M. B. (1989). Vasodilation and reduction in forearm vascular resistance after acute administration of dilevalol. *Am. J. Cardiol.*, **63**, 171–201.
- Lennard, M. S. (1991). Clinical pharmacology through the looking glass: reflection on the racemate vs enantiomer debate. *Br. J. clin. Pharmacol.*, **31**, 623–625.
- Lund Johanson, P. (1988). Haemodynamic effects of β blocking compounds possessing vasodilating activity: a review of labetalol, prazosin and dilevalol. *J. cardiovasc. Pharmacol.*, **11** (suppl. 2), S12–S17.
- MacLennan, B. A., Riddell, J. G. & Shanks, R. G. (1989). The selectivity of the partial agonist activity of dilevalol in man. *Clin. Pharmacol. Ther.*, **45**, 168.
- Pocock, S. J. (1984). *Clinical trials; a practical approach*. Chichester: Wiley & Son.
- Roberts, D.H., Tsao, Y. & Breckenridge, A.M. (1986). The reproducibility of limb blood flow measurements in human volunteers at rest and after exercise by using mercury in silastic strain gauge plethysmography under standardised conditions. *Clin. Sci.*, **70**, 635–638.
- Roberts, D. H. (1990). *Peripheral haemodynamic effects of antihypertensive agents*. MD thesis, University of Liverpool.
- Roberts, D. H., Tsao, Y., Grimmer, S., Winstanley, P. A., Orme, M. & Breckenridge, A. M. (1987). Haemodynamic effects of atenolol, labetalol, pindolol and captopril: a comparison in hypertensive patients with special reference to changes in limb blood flow, heart rate and left ventricular function. *Br. J. clin. Pharmacol.*, **24**, 163–172.
- Schoenberger, J., Frishman, W., Wallin, J. D. *et al.* (1989). Dilevalol compared with propranolol and placebo for systemic hypertension. *Am. J. Cardiol.*, **63**, 451–491.
- Silagy, C. A., McNeil, J. J., Farish, S. & McGrath, B. P. (1990). A comparison of dilevalol and placebo in the management of isolated systolic hypertension using ambulatory monitoring. *Br. J. clin. Pharmacol.*, **30**, 657–664.
- Strom, J. A., Vidt, D. G., Bugni, W. *et al.* Mechanism of antihypertensive action of dilevalol compared to that of cardioselective beta-blocking agents. *Am. J. Cardiol.*, **63**, 251–331.
- Sybertz, E. J., Sabin, C. S., Pula, K. K. *et al.* (1981). Alpha and beta adrenoceptor blocking properties of labetalol and its R,R isomer SCH 19927. *J. Pharmacol. exp. Ther.*, **218**, 435–443.
- Vaccarella, A., Lissoni, F., Scarpazza, P., Cavallotti, G., Calabresi, N. & Mazzola, C. (1989). Comparative effects of dilevalol and nifedipine on 24 hr pressure profiles in mild to moderate hypertension. In *Beta₂ partial agonism in the treatment of hypertension; results with dilevalol*. Satellite to the Fourth European meeting on hypertension, p. 31. Macclesfield: Adelphi Communication.
- Waller, D. (1990) β -adrenoceptor partial agonists: a renaissance in cardiovascular therapy? *Br. J. clin. Pharmacol.*, **30**, 157–171.

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