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The effect of slow-release nicardipine on ambulatory and clinic blood pressure in mild hypertension

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1 The antihypertensive efficacy of a long acting formulation of the calcium channel blocking drug, nicardipine, was assessed using clinic and ambulatory (Remler M2,000) blood pressure measurements.

2 Eleven patients with essential hypertension (mean ± s.e. mean; 173 ± 6.6/103 ± 1.9 mmHg) completed a randomised double-blind, placebo-controlled, cross-over study. The dose of nicardipine used was 60 mg twice daily for 4 weeks.

3 Mean ambulatory blood pressure was reduced from 164 ± 5.3/97 ± 2.9 to 151 ± 5.2/88 ± 2.4 mmHg ($P < 0.01$); this effect was shown to be sustained for 8 h after the morning dose. Mean ambulatory heart rate was not significantly affected by treatment.

4 Clinic lying systolic blood pressure was reduced on treatment from 169 ± 7.1 to 157 ± 5.9 mmHg ($P < 0.2$) and diastolic blood pressure from 99 ± 3.6 to 89 ± 3.9 mmHg ($P < 0.05$).

5 One patient was withdrawn because of dizziness and flushing while on nicardipine; vasodilatory side effects such as headache, palpitations and flushing on nicardipine were noted by three patients.

6 We conclude that the long acting formulation of nicardipine studied in a dose of 60 mg twice daily is effective as monotherapy and is relatively well tolerated in mild hypertension.

7 This study highlights the importance of ambulatory blood pressure measurement in detecting significant changes in blood pressure, thereby permitting the study of small numbers of patients.

Keywords ambulatory blood pressure measurement hypertension nicardipine calcium channel blockers

Introduction

Nicardipine is a new dihydropyridine derivative, closely related to nifedipine in chemical structure and action (Seki & Takenaka, 1977). It has been shown to be effective in hypertension when assessed using clinic blood pressure measurements in uncontrolled (Takabatake *et al.*, 1982; Taylor *et al.*, 1985) and short-term controlled trials (Asplund, 1985; Bellet *et al.*, 1985). Moreover, nicardipine in a dose of 40 mg twice daily has been shown in an open study to have a sustained antihypertensive effect as assessed by direct intra-arterial monitoring but with a high incidence of side effects (Jones *et al.*, 1983), possibly because of the high peak plasma levels associated with the standard-formulation used. A new formulation of nicardipine (containing 30 mg standard and 30 mg slow-release pellet formulations of nicardipine) has been designed

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with the object of providing a sustained antihypertensive effect between doses when given twice daily but with fewer side effects. The aim of this study was to assess the efficacy of this formulation of nicardipine in a randomized double-blind placebo-controlled cross-over study using ambulatory blood pressure recordings in addition to clinic measurements. Drug absorption was assessed by measuring plasma nicardipine levels before and 2 h after dosing.

Methods

Twelve patients (eight female, four male, age range 32–65 years) with a lying diastolic blood pressure of 95 mmHg or greater were studied. Women who were pregnant or lactating and patients on drug therapy for any other illness were excluded. The study protocol was approved by the hospital ethics committee and informed consent was obtained.

Study design

Patients whose lying diastolic blood pressure remained within the limits of 95–110 mmHg after a 4 week-run-in phase on placebo entered a randomised double-blind, placebo-controlled, cross-over study. Nicardipine in capsules was given in a dose of 60 mg (30 mg standard formulation and 30 mg slow release pellet formulation) twice a day, taken at 09.00 and 21.00 h. Treatment periods lasted 4 weeks and were separated by a 4 week wash-out period on placebo. Patients were seen every 4 weeks for measurement of blood pressure. In addition at the end of each treatment period ambulatory blood pressure and heart rate recordings were made. Plasma samples were taken for nicardipine levels before and 2 h after dosing.

Methods

Ambulatory blood pressure and heart rate were measured non-invasively at half-hourly intervals using a semi-automated portable recorder, the Remler M2,000 (Remler Corp. San Francisco, C.A.), which is reliable and accurate (Fitzgerald *et al.*, 1982). The machine was operated by the patient from 09.00 to 22.00 h. All tapes were decoded by one operator. Clinic blood pressure was measured between 11.00 and 12.00 h with the Hawksley random zero sphygmomanometer, Korotkov phase V being taken for diastolic pressure. Recordings were made with the patient lying after 5 min rest and standing after 2 min with the arm supported at heart level (Petrie *et al.*, 1986).

Plasma samples were taken before and 2 h after dosing at the end of each treatment period and stored at −20° C prior to assay for nicardipine levels by high-performance liquid chromatography (Wu *et al.*, 1984). The lower limit of sensitivity of the assay was 1 ng ml^{-1}.

Side effects were assessed during treatment periods by means of a check-list on which patients were asked to grade symptoms on a scale from 0–3 on a daily basis. In addition, at the end of each treatment period patients were given the opportunity to describe any further symptoms experienced during treatment.

Ambulatory blood pressure and heart rate were analysed using a computer programme designed to pair half-hourly readings on nicardipine with readings for the same time of day on placebo. Unpaired data were omitted. Average values for ambulatory blood pressure and heart rate were computed for each patient on nicardipine and on placebo. The means of two clinic readings for lying and standing blood pressure were used. Student's paired *t*-test was used for all comparisons and the influence of treatment, order and interaction effects were determined by the method appropriate for cross-over studies suggested by Hills & Armitage (1979). A probability value of less than 5% was taken to be significant.

Results

One patient was withdrawn from the study (see below), leaving seven females and four males, mean age 51.7 years and range 32–65 years. Mean ± s.e. mean clinic lying blood pressure at the end of the placebo run-in phase was 173 ± 6.6/103 ± 1.9 mmHg. Nicardipine significantly reduced clinic lying diastolic pressure only (Table 1). There were no period or interaction effects.

Mean ambulatory blood pressure was reduced from 164 ± 5.3/97 ± 2.9 to 151 ± 5.2/88 ± 2.4 mmHg (treatment difference 13 ± 3.8/9 ± 2.8 mmHg; $P < 0.01$) on treatment with nicardipine. This effect was apparent within 2 h of the morning dose and was sustained for 8 h (Figure 1), while mean ambulatory heart rate was unchanged with treatment (74.6 *vs* 76.7 beats min^{-1} on nicardipine).

Mean (± s.e. mean) plasma nicardipine levels 2 h after dosing were 28.6 ± 5.9 ng ml^{-1} (range 5.7 to 60.6 ng ml^{-1}) and were 7.3 ± 3.0 ng ml^{-1} (range 3.7 to 14.3 ng ml^{-1}) in samples taken before dosing. There was no correlation between changes in systolic and diastolic blood pressure and nicardipine levels 2 h after dosing.

Table 1 Clinic blood pressure on placebo or nicardipine (values are mean ± s.e. mean; $n = 11$)

		Placebo	*Nicardipine*	*Treatment difference*	*95% confidence interval*
Lying BP (mmHg)	Systolic	169 ± 7.1	157 ± 5.9	10.6 ± 6.0	−3.0 : 24.2
	Diastolic	99 ± 3.6	89 ± 3.9	10.7 ± 3.9*	1.7 : 19.7
Standing BP (mmHg)	Systolic	157 ± 8.6	151 ± 5.4	4.6 ± 10.2	−18.8 : 27.7
	Diastolic	97 ± 3.4	93 ± 3.4	3.9 ± 3.7	−2.1 : 10.0

*$P < 0.05$.

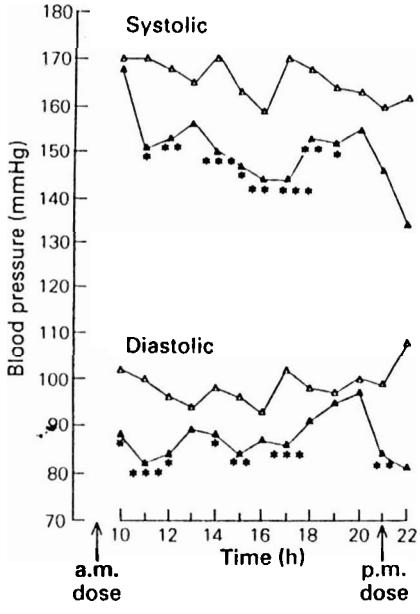

Figure 1 Curves derived from the means of hourly values of ambulatory systolic and diastolic blood pressure on placebo (△) and nicardipine (▲) after 4 weeks of treatment. $n = 11$; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

One patient was withdrawn from the study after 10 days on nicardipine because of dizziness and flushing. Vasodilatory side effects such as headache, palpitations and flushing on nicardipine were noted by three patients.

Discussion

Ambulatory blood pressure measurement demonstrated a significant blood pressure lowering effect which was sustained for 8 h with nicardipine 60 mg twice daily. This was achieved without any effect on heart rate. Furthermore this formulation of nicardipine was reasonably well tolerated apart from the one patient who withdrew from the study. The duration of antihypertensive effect of the new formulation of nicardipine in a dose 60 mg twice daily is similar to that reported for the standard formulation in a dose of 40 mg twice daily (Jones *et al.*, 1983) but with fewer side effects. A similar long-acting formulation of nicardipine (nicardipine LA) containing 25% fast release and 75% slow release pellets in a dose of 50 mg twice daily in a randomised placebo-controlled cross-over study was also shown to have a sustained antihypertensive effect as assessed by both clinic and ambulatory blood pressure monitoring with few side effects (Bellet *et al.*, 1987). From these studies with small numbers of patients it would appear that long acting formulations of nicardipine may reduce the incidence of side effects associated with high peak plasma concentrations of the drug while at the same time producing a sustained antihypertensive effect over the dosing interval.

To judge from the plasma levels absorption of the 60 mg dose of nicardipine appears to be gradual. Single oral doses of 30 mg of the standard formulation of nicardipine have been shown to give peak plasma levels of up to 100 ng ml^{-1} between 20 min and 2 h after dosing (Graham *et al.*, 1984) whereas the highest 2 h level in the present study was only 60.6 ng ml^{-1}.

Although the magnitude of the fall of blood pressure in our study was similar with both clinic and ambulatory measurement, the reduction of clinic blood pressure was statistically significant only for lying diastolic pressure. The failure of conventional measurement to detect a clinically significant blood pressure lowering effect when ambulatory measurement does, has been reported in several other small studies (Gould *et al.*, 1981; O'Boyle *et al.*, 1984; Schaller *et al.*, 1985). Because of the paucity of data, the power of clinic readings to detect statistically significant change was limited, whereas, ambulatory measurement with the greater number of observations available, increased the power of these studies, mainly by reducing within-subject variability.

Applying the power calculations for cross-

over studies described by Hill & Armitage (1979) to the data in this study, eight patients would be required if ambulatory measurement was used to assess blood pressure lowering effect (to achieve a power of 85%), whereas 30 patients would be needed with clinic measurement. Given the increasing demands for and the high costs of studies of blood pressure lowering agents, the potential of ambulatory blood pressure to detect clinically significant reductions using smaller samples than those required using clinic measurement has important logistical implications (Conway *et al.*, 1988).

In conclusion the long acting formulation of nicardipine in a dose of 60 mg twice daily provided control of blood pressure with a reduction in day-time ambulatory blood pressure of 13/9 mmHg which was sustained for the greater part of the dosing interval with relatively few side effects. More importantly however, this study highlights the importance of ambulatory blood pressure measurement in the assessment of antihypertensive drug efficacy. Using this method it may be possible to reduce markedly the number of patients required in such studies.

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References

Asplund, J. (1985). Nicardipine hydrochloride in essential hypertension—a controlled study. *Br. J. clin. Pharmac.*, **20**, 120S–124S.

Bellet, M., Loria, Y. & Lallemand, A. (1985). First-step treatment of mild to moderate uncomplicated essential hypertension by a new calcium antagonist: nicardipine. *J. cardiovasc. Pharmac.*, **7**, 1149–1153.

Bellet, M., Pagny, J-Y., Chatellier, G., Corvol, P. & Menard, J. (1987). Evaluation of slow release nicardipine in essential hypertension by casual and ambulatory blood pressure measurements. Effects of acute versus chronic administration. *J. Hypertension*, **5**, 599–604.

Conway, J., Johnston, J., Coats, A., Somes, V. & Sleight, P. (1988). The use of blood pressure monitoring to improve the accuracy and reduce the numbers of subjects in clinical trials of antihypertensive agents. *J. Hypertension*, **6**, 111–116.

Fitzgerald, D. J., O'Callaghan, W. G., McQuaid, R., O'Malley, K. & O'Brien, E. (1982). Accuracy and reliability of two indirect ambulatory blood pressure recorders: Remler M2, 000 and Cardiodyne Sphygmolog. *Br. Heart J.*, **48**, 572–579.

Gould, B. A., Mann, S., Davies, A., Altman, D. G. & Raftery, E. B. (1981). Indormin: 24-hour profile of intra-arterial ambulatory blood pressure, a double-blind placebo-controlled cross-over study. *Br. J. clin. Pharmac.*, **12**, 675–735.

Graham, D. J. M., Dow, R. J., Freedman, D., Mroszczak, E. & Ling, T. (1984). Pharmacokinetics of nicardipine following oral and intravenous administration in man. *Postgrad. med. J.*, **60**, (suppl. 4), 7–10.

Hills, H. & Armitage, P. (1979). The two-period cross-over clinical trial. *Br. J. clin. Pharmac.*, **8**, 7–20.

Jones, R. I., Hornung, R. S., Sonecha, T. & Raftery, E. B. (1983). The effect of a new calcium channel blocker nicardipine on 24-hour ambulatory blood pressure and the pressor response to isometric and dynamic exercise. *J. Hypertension*, **1**, 85–89.

O'Boyle, C., Fitzgerald, D., Kelly, J. G., O'Malley, K. & O'Brien, E. (1984). The efficacy of indapamide in hypertensive patients failing to respond to β-blocker alone. *Drugs of Today*, **20**, 27–31.

Petrie, J. C., O'Brien, E. T., Littler, W. A. & de Swiet, M. (1986). British Hypertension Society. Recommendations on blood pressure measurement. *Br. med. J.*, **293**, 611–615.

Schaller, M. D., Nussberger, J., Waeber, B., Porchet, M. & Brunner, H. R. (1985). Transdermal clonidine therapy in hypertensive patients. *J. Am. med. Ass.*, **253**, 233–235.

Seki, T. & Takenaka, T. (1977). Pharmacological evaluation of YC—93, a new vasodilator, in healthy volunteers. *Int. J. clin. Pharmac.*, **15**, 267–274.

Takabatake, T., Ohta, H., Yamamoto, Y., Maekawa, M., Arai, S., Hattori, N. & Nomura, G. (1982). Antihypertensive effect of nicardipine hydrochloride in essential hypertension. *Int. J. clin. Pharmac. Ther. Tox.*, **20**, 346–352.

Taylor, S. H., Frais, M. A., Lee, P., Verma, S. P., Jackson, N., Reynolds, G. & Silke, B. (1985). A study of the long-term efficacy and tolerability of oral nicardipine in hypertensive patients. *Br. J. clin. Pharmac.*, **20**, 139S–142S.

Wu, A. T., Massey, I. J. & Kushinsky,S. (1984). A high-performance liquid chromatographic method for the simultaneous determination of nicardipine and its pyridine metabolite 11 in plasma. *J. pharm. Sci.*, **73**, 1444–1447.

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