Nicardipine hydrochloride in essential hypertension — a controlled study

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1 Fifty patients with mild essential (primary) hypertension entered a double-blind, parallel-group study with either nicardipine 30 mg three times daily or placebo, randomly assigned as monotherapy for 6 weeks.

2 At the end of 6 weeks, the nicardipine-treated group had a statistically significant reduction in mean supine systolic/diastolic pressure of 21.2/15.0 mm Hg ($P < 0.001$) compared with the nonsignificant reduction of 0.7/2.9 mm Hg in the placebo-treated group. The difference in mean response between the nicardipine- and placebo-treated groups was significant ($P < 0.001$).

3 In the nicardipine-treated group, the reduction in mean standing systolic/diastolic blood pressure, 17.9/13.8 mm Hg, was significant ($P < 0.001$), whereas in the placebo-treated group the change was +3.0/–1.5 mm Hg. The difference between the two treatment groups was significant ($P < 0.001$).

4 In both treatment groups, changes in pulse rate were minor, and there was no evidence of tachyphylaxis occurring with nicardipine. Adverse experiences were minor in all cases except for one patient with muscle pain during treatment with nicardipine.

5 Patients who received nicardipine showed a mean increase of 52% in plasma renin activity (PRA) after 6 weeks ($P < 0.01$). Initial basal or stimulated PRA did not correlate with blood pressure reduction on nicardipine.

6 Nicardipine 30 mg three times daily is a well-tolerated and effective antihypertensive agent.

Keywords age hypertension nicardipine plasma renin activity

Introduction

It is accepted that in essential (primary) hypertension the principal haemodynamic disturbance is increased total peripheral resistance (Lund-Johansen, 1980). A logical approach to therapy would use drugs that reduce this increased resistance, although it is still not known if this has a favourable effect on the prognosis. Some vasodilators tend to cause reflex tachycardia, salt and water retention, tachyphylaxis, and postural hypotension (Koch-Weser, 1974).

Calcium channel blockers act as vasodilators, thereby reducing blood pressure (Lewis *et al.*, 1978; Olivari *et al.*, 1979). The reduction in blood

pressure that occurs with some calcium antagonists seems to correlate with the level of pre-treatment plasma renin activity (PRA) and the age of the patient (Bühler *et al.*, 1982).

Nicardipine, a new calcium antagonist, has been shown to be an effective hypotensive agent (Jones *et al.*, 1983); in this study the hypotensive effect of 30 mg given three times a day has been compared with that of placebo in patients with mild, essential hypertension. The relationship between hypotensive effect, PRA, and patient age also has been examined.

Methods

There were 36 male and 14 female patients with a mean age of 46 years (range 36–60 years). Forty-seven patients were categorised as WHO disease stage I, and three patients were in disease stage II. Before entering the study, 17 patients were being treated with either a β -adrenoceptor blocking drug or a thiazide diuretic, three patients were receiving a combination of these drugs, and 30 were untreated. The diagnosis of primary hypertension was confirmed in all patients by history, clinical and laboratory investigation.

On admission to the study all previous therapy was stopped, and the patients had a treatment-free run-in period of 4 weeks. If the supine diastolic blood pressure was in the range of 95–115 mm Hg on three visits during this run-in phase, the patients were judged to have stable essential hypertension and were eligible for the comparative treatment portion of the study.

At the third visit these patients received either nicardipine 30 mg three times daily or a placebo

capsule of identical appearance. The blood-pressure measurements were performed by the same person, at the same time of the day for each patient, using the same random zero sphygmomanometer. Each patient was treated for 6 weeks, with clinic visits every second week. Adverse experiences during treatment were reported in response to the nonspecific questions: 'How have you been since I last saw you? Do the capsules suit you?'

Laboratory monitoring measurements made before and at the end of treatment, included a complete blood count, ESR, and analyses of serum sodium, potassium, calcium, creatinine, albumin, ASAT, ALAT, ALP, LDH, bilirubin, thyroxine, triiodothyronine and TSH. Before admission, upright PRA, before and after frusemide 80 mg, was measured by radioimmunoassay (Fyhrquist *et al.*, 1976). Unstimulated PRA also was measured at the end of treatment. The ECG for each patient was recorded at the start and at the end of the study. Compliance with treatment was assessed by a returned capsule count at each visit. The study protocol was approved by the Uppsala Ethics Committee, and all patients gave their informed consent to participate in the study. Student's *t*-test for paired data was used for the comparison of results within the treatment groups, and the *t*-test for unpaired data was used for comparisons between treatment groups.

Results

Patients in the nicardipine and placebo treatment groups were equally matched for age and sex, admission blood pressure, previous therapy, and WHO disease stage. Females in the placebo treatment group were, on the average, 15 kg heavier and 5 years older than those in the nicardipine group, but these differences were not statistically significant.

For reasons that were not related to the therapy, three patients were withdrawn from the study before the last visit. Two of these patients had received nicardipine, and one had received placebo.

As shown in Figure 1, after 6 weeks of treatment with nicardipine, the mean supine systolic blood pressure had fallen by 21.2 mm Hg and the mean diastolic pressure by 15 mm Hg; these differences are significant ($P < 0.001$). In the patients who received placebo for 6 weeks, the mean supine systolic blood pressure had fallen by

Figure 1 Mean supine blood pressure and heart rate after placebo (□) or nicardipine (■). * $P < 0.01$, ** $P < 0.001$.

Figure 2 Mean standing blood pressure and heart rate after placebo (□) and nicardipine (■). * $P < 0.01$, ** $P < 0.001$.

0.7 mm Hg and the mean diastolic pressure by 2.9 mm Hg; these differences are not significant ($P > 0.05$). The difference in mean response between active treatment and placebo is also significant ($P < 0.001$).

Changes in the mean standing blood pressure measurements are shown in Figure 2. After 6 weeks, patients who received nicardipine showed a reduction in systolic/diastolic pressures of 17.9/13.8 mm Hg ($P < 0.001$). Patients who received placebo showed an increase in mean systolic pressure and a reduction in diastolic pressure of +3.0/−1.5 mm Hg; the difference between the response in the two treatment groups is significant ($P < 0.001$). Changes in the mean pulse rate are shown in Figures 1 and 2; in neither treatment group was there any change of clinical significance. During these 6 weeks there was no evidence of tachyphylaxis to nicardipine.

Adverse experiences

Fifteen patients in the nicardipine-treated group and 10 in the placebo-treated group reported adverse experiences (Table 1). No patients were withdrawn from the study because of their reported experiences. One patient who received nicardipine reported 'severe' muscle pains in the arms; these resolved even with continued nicardipine treatment.

Table 1 Adverse experiences

Number of patients reporting...	Nicardipine 15			Placebo 10		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Headache	1	—	—	—	1	—
Tiredness	1	2	—	—	1	—
Vertigo	—	—	—	—	1	—
Irritability	—	—	—	1	—	—
Flushing	4	3	—	1	—	—
Palpitations	1	1	—	3	—	—
Ankle oedema	—	1	—	—	—	—
Retrosternal pain	—	—	—	1	—	—
Diarrhoea	—	—	—	1	—	—
Constipation	1	1	—	—	—	—
Increased appetite	1	—	—	—	—	—
Itching	—	—	—	1	—	—
Muscle pain	2	—	1	—	—	—
Impotence	—	—	—	—	1	—
Increased frequency of micturition	1	1	—	—	1	—

Table 2 Plasma renin activity (pkat l^{-1}), mean $\pm$ s.d.

	Nicardipine group	Placebo group
Basal, on admission (n =)	0.27 $\pm$ 0.14 (25)	0.13 $\pm$ 0.22 (23)
Stimulated, on admission (n =)	0.40 $\pm$ 0.26 (26)	0.51 $\pm$ 0.34 (24)
Basal on termination (n =)	0.42 $\pm$ 0.26* (23)	0.30 $\pm$ 0.24 (24)

* $P < 0.01$.

Laboratory monitoring

Patients for whom laboratory tests yielded values that fell outside laboratory reference range were found to be equally distributed between placebo and nicardipine groups. Indeed, patients who were so listed post-treatment were, in most cases, those who also were listed prior to treatment. There were no significant or relevant changes in the ECG and no changes in PRQ, QRS, or QT intervals.

Mean values of PRA are shown in Table 2. At the end of treatment, the patients who received nicardipine showed a mean increase of 52% in PRA; this difference from baseline, as well as the difference between the nicardipine- and placebo-treated groups is significant, ($P < 0.01$).

Age

Correlation between changes in blood pressure, pulse rate, and age was assessed by fitting generalized linear models. There was no relationship between increasing age and drug effect on blood pressure or pulse rate when the nicardipine-treated group was compared with the placebo-treated group. However, patients who received nicardipine showed a correlation between systolic pressure change, both supine and standing, and the standing diastolic pressure change.

Discussion

The results of this study show that nicardipine, 30 mg three times daily is an effective hypotensive agent, comparable with standard doses of β -adrenoceptor blockers (Asplund, 1981), thiazides (Multicentre Diuretic Co-operative Study Group, 1981), verapamil (Gould *et al.*, 1981), and

nifedipine (Pederson *et al.*, 1979). In an open study Takabatake *et al.* (1982) obtained a reduction in mean systolic/diastolic blood pressure of 17.8/14.2 mm Hg after 4 weeks of treatment with nicardipine 10 mg three times daily – one third of the dose used in the present study. Perhaps this may be explained by an additive placebo effect or by the fact that their patients were smaller in size. In an uncontrolled study of six patients, Taylor and his colleagues (1982) used nicardipine 20 mg three times daily for 2 weeks and found a mean reduction in blood pressure of 23/15 mm Hg. These workers also found that nicardipine had no effect on the pressure response to isometric exercise, dynamic exercise, or cold stimulation. This could be expected since nicardipine, like the other calcium channel blockers, has no effect on sympathetic drive, and this suggests that a combination of calcium blockade and β -adrenoceptor blockade could be useful.

In the present study, nicardipine did not produce any clinically significant change in heart rate; the tachycardia often seen in association with vasodilators was probably ameliorated by resetting of the baroreceptor mechanism as described by Young *et al.* (1984).

The hypotensive effect of nicardipine did not show any correlation with the pretreatment-stimulated PRA, which is in agreement with the results obtained with nifedipine by Öhman and others (1985). There was a significant rise in PRA after treatment with nicardipine, which also was reported by Takabatake *et al.* (1982) and which was seen by Öhman *et al.* (1985), and Pedersen *et al.* (1979) with nifedipine. This increase in PRA may be caused by vasodilatation-stimulating baroreflex mediation of renin release. Bühler *et al.* (1982) reported that verapamil is a more effective antihypertensive agent in older age patients and in those with lower PRA. In this

study there was no correlation between initial, basal or stimulated, PRA and blood pressure reduction on nicardipine. There was however a correlation between increasing age and systolic pressure change, both supine and standing, and the standing diastolic change in the nicardipine group.

Other workers (Bala Subramanian & Raftery, 1981) demonstrated that nicardipine 20 mg three

times daily gave rise to fewer adverse experiences than did verapamil 120 mg three times daily or nifedipine 10–20 mg three times daily. In this study the adverse experiences reported by the nicardipine-treated patients generally were mild. In conclusion, the results of this study have shown nicardipine 30 mg three times daily to be an effective and well-tolerated hypotensive agent.

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