A study of the long-term efficacy and tolerability of oral nicardipine in hypertensive patients

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1 This study was designed to evaluate the efficacy of oral nicardipine in 91 patients with uncomplicated essential hypertension over a period of 12 months. All patients started on a fixed nicardipine dose of 30 mg three times daily which was adjusted in the range 10–40 mg three times daily, where necessary to achieve a target diastolic blood pressure < 95 mm Hg.

2 At 6 weeks, blood pressure (mean $\pm$ s.e. mean) was reduced from an average of $190 \pm 22/112 \pm 8$ to $167 \pm 23/96 \pm 11$ mm Hg supine and from $180 \pm 21/113 \pm 7$ to $154 \pm 17/95 \pm 11$ mm Hg standing and remained controlled in all patients throughout the study.

3 A total of 96 unwanted experiences were reported by 49 patients (54%); 17 (19%) reported a single symptom once and two (2%) reported a single symptom more than once. The most frequently reported adverse experiences were peripheral oedema in 27 (28%) and headaches in 15 patients (16%).

4 The majority of the adverse experiences occurred in the first 3 months of treatment. Ten patients (11%) withdrew from the study during this time and eight (9%) in the subsequent 9 months because of drug-related side effects; five others (5%) withdrew for unrelated reasons.

5 The incidence of adverse experiences was dose-related. Three patients reported unwanted effects on 10 mg three times daily, eight on 20 mg three times daily, 36 on 30 mg three times daily, and 12 on 40 mg three times daily oral nicardipine.

6 The relatively high incidence of reported adverse experiences may reflect the fact that there was no comparative placebo control group and that patients were encouraged to report all adverse experiences.

Keywords nicardipine efficacy hypertension tolerability

Introduction

Many drugs with powerful blood-pressure-lowering activity are now available for the treatment of hypertensive patients. Their overall efficacy is dictated as much by their tolerability during chronic administration as by their antihypertensive potency. Nicardipine clearly has blood-pressure-lowering activity (Taylor *et al.*, 1981, 1985). The following study was designed, therefore, to evaluate its tolerability when given in constant dose, without other antihypertensive drugs, to hypertensive patients for a minimum of 1 year.

Methods

Patient population

Ninety-one white patients (18 male, 73 female), aged 23–70 years, with stable essential hypertension (average blood pressure supine $190 \pm 22/112 \pm 8$ mm Hg and standing $180 \pm 21/113 \pm 7$ mm Hg (mean $\pm$ s.d.)) were included in the study. Pregnant or lactating females and patients with angina pectoris, myocardial infarction in the previous 6 months, radiographic evidence of heart failure, second degree or greater atrioventricular conduction block, cardiac arrhythmias, grade 3 or 4 retinal hypertensive changes,

diabetes mellitus, or abnormal haematological, renal, hepatic, or thyroid laboratory tests were excluded. Previous hypertensive therapy was discontinued at least 2 weeks before the start of nicardipine therapy. Informed consent was obtained from each patient, and the study was approved by the hospital Ethics Committee.

Study design

The design was an open evaluation of the incidence of unwanted side effects over a period of 12 months in patients taking only nicardipine for control of their blood pressure. Patients attended the Hypertension Clinic 2 weeks before the start of the study and at weeks 0, 2, and 6 and at months 3, 6, 9, and 12.

At each attendance, supine and standing blood pressure and heart rate were measured in triplicate after 10 min of rest. Haematology, plasma biochemistry, and urine constituents were monitored at each visit and, in each patient, a 12-lead ECG recorded at the start and end of the study. Reports of side effects were obtained by asking nonspecific questions during each visit,

and the patients were encouraged to report all adverse experiences. Patients started with an oral dose of nicardipine 30 mg three times daily, which was adjusted in relation to their blood pressure control within the dose-range 10–40 mg three times daily.

Laboratory techniques and measurements

Blood pressure was measured in the right arm by random zero sphygmomanometer (Hawksley-Gelman; Korotoff Phase V diastolic component). Heart rate was measured by arterial palpation.

Results

Blood-pressure control (Figure 1)

In 91 patients, by the end of the 6 week dose-adjustment period, blood pressure was reduced from $190 \pm 22/112 \pm 8$ to $167 \pm 23/96 \pm 1$ mm Hg supine and from $180 \pm 21/113 \pm 7$ to $154 \pm 17/95 \pm 11$ mm Hg standing. The nicardipine dose then remained unchanged for each patient for the rest of the study.

Figure 1 Supine and standing systemic blood pressure (mean $\pm$ s.e. mean) during control period (C) and during the study. The number of patients for whom data were available is shown below:

	Time (Months)					
	Control	1.5	1.5–3	3–6	6–9	9–12
Supine	91	91	43	73	70	73
Standing	62	62	22	55	59	73

Table 1 Number adverse experiences reported by 49 patients: some patients reported more than one adverse experience

	Number	%
Peripheral oedema	27	(28)
Headache	15	(16)
Dizziness	6	(6)
Rash	6	(6)
Fatigue	5	(5)
Myalgia	5	(5)
Dyspepsia	4	(4)
Vasodilatation	4	(4)
Angina	3	(3)
Palpitations	3	(3)
Dyspnoea	3	(3)
Others	15	(16)
Total	96	

Adverse experiences (Table 1)

At total of 96 adverse experiences were reported by 49 patients (54%). Seventeen patients (19%) reported a single symptom once, and two (2%) reported a single symptom more than once. Ten patients (11%) were withdrawn from treatment within the first 3 months and eight (9%) between 3 and 12 months because of unwanted effects; five others (5%) were lost to follow-up for unrelated reasons.

Twenty-one patients reported adverse experiences within the first 2 weeks of starting nicardipine, 23 between 2 and 12 weeks of treatment, and 19 after this time.

The most frequently reported experiences were peripheral oedema in 27 (30%) and headaches in 15 (16%) patients. The 18 patients who were withdrawn from treatment because of unwanted effects included eight with peripheral oedema and five with headaches.

Three patients experienced the onset of adverse reactions to oral nicardipine at a dose of 10 mg three times daily, eight at a dose of 20 mg three times daily, 36 at a dose of 30 mg three times daily, and 12 at a dose of 40 mg three times daily.

While in the study, one patient died from myocardial infarction.

Discussion

Calcium antagonists have been advocated as combination therapy or even first-line monother-

apy for the treatment of essential hypertension (Gould *et al.*, 1983; Erne *et al.*, 1983). They have been reported to be well tolerated and to lack many of the side-effects of other popular anti-hypertensive drugs, such as the biochemical disorders associated with thiazide diuretics (Amery *et al.*, 1978; Grimm *et al.*, 1981) or the side effects of lethargy, cold extremities, and bronchospasm following β -adrenoceptor antagonists (Besterman, 1983). However, the information regarding tolerability of the calcium-entry blocking drugs has been derived from relatively small studies in which their blood-pressure lowering ability was the prime objective. Few large-scale studies have been devoted specifically to determining tolerability to their long-term administration.

In the present study, 49 of 91 patients experienced a total of 96 adverse reactions; most of these occurred in the first 3 months of treatment. The most frequently reported problems were peripheral oedema and headaches. Others included dyspepsia, dizziness, skin rash, and vasodilatation, all of which have been recognised as complications of treatment with other calcium antagonists. The incidence of ankle swelling in our patients was, however, greater than the 0.67% of 4,863 patients reported in a collected review of all studies with calcium-entry blocking drugs (Ebner *et al.*, 1980).

There are many disadvantages inherent in a study designed to highlight the character and incidence of unwanted reactions, particularly in asymptomatic patients. Concentration on this aspect naturally leads to documentation of many unwanted effects despite the potential benefits of adequate blood-pressure control.

Although there was a relatively high incidence of adverse experiences reported, this study confirms the antihypertensive effectiveness of nicardipine during long-term administration. It is quite likely that this incidence of adverse experiences reflects problems in the study design. Further studies obviously are necessary to investigate the short- and long-term tolerability of this drug in the treatment of essential hypertension, particularly when used in combination with other common antihypertensive drugs.

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