The effect of nicardipine on blood pressure, its variability and reflex cardiac control

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1 Eight untreated patients with essential hypertension (average casual blood pressure 180/110 ± 27/12 mm Hg) were studied following control, acute (a single oral dose of 30 mg nicardipine hydrochloride), and chronic (2 months nicardipine oral therapy) treatment periods.

2 During the 2 month treatment period, ambulatory mean intra-arterial (IABP), measured when the patients were awake, fell from 165/105 ± 6/12 (control) to 150/96 ± 14/12 mm Hg (P < 0.05), but heart rate remained unchanged (84 ± 12 control vs 80 ± 9 beats min⁻¹).

3 There was an absolute reduction in blood pressure in response to tilting, the Valsalva manoeuvre, and exercise handgrip, but the percent increase in pressure following nicardipine was not significantly different from that in the control period.

4 There was no change in baroreflex sensitivity after either acute or chronic treatment, but the set point of the reflex was reset to a lower pressure following chronic therapy.

5 Both single and multiple doses of nicardipine significantly reduced intra-arterial pressure. Chronic therapy was associated with return of the heart rate to control values, which was due to resetting of the baroreflex control mechanism.

Keywords ambulatory blood pressure monitoring baroreflexes hypertension calcium channel blockers

Introduction

Nicardipine is a calcium channel blocker similar to nifedipine in structure and actions. It has been reported to have no effects on the sino-atrial and atrio-ventricular nodes and no direct effects on the myocardium. Nicardipine has a serum half-life of 7–8 h after multiple-dosing in man. In this study we assessed the efficacy of nicardipine as a hypotensive agent during ambulatory intra-arterial blood pressure monitoring and cardiovascular reflex testing. The assessment of baroreflex sensitivity after nicardipine has been described in detail by us (Young et al., 1984).

Methods

We studied eight patients with essential hypertension who had no evidence of target organ damage. Essential hypertension was defined as three separate outpatient cuff pressures of 140/90 mm Hg or more after 5 min supine rest (Phase V diastolic). Five patients were male, three were female, and their average age was 49 years (range 36–64 years). The average outpatient clinic cuff pressure for the group was 180/100 ± 27/12 mm Hg (± s.d.).

Intra-arterial pressure was measured from the brachial artery in the patient’s non-dominant arm, by a 1 mm diameter Teflon cannula which was connected via a transducer and perfusion pump to a miniature analogue tape recorder. Heart rate was recorded onto the same apparatus (Littler et al., 1972).

Following beat-to-beat computer analysis of the tapes, the intra-arterial blood pressure profile was divided into waking and sleeping periods, the latter being taken from the time of retirement to
the time of arousal, as indicated on diary cards. Blood pressure variability was measured as the standard deviation of a normally distributed frequency histogram (Watson et al., 1979).

**Cardiovascular reflexes**

On each occasion these were measured in a quiet laboratory during the morning. Intra-arterial blood pressure and heart rate were recorded simultaneously on a Grass polygraph 70 physiological recorder connected to the arterial cannula via a miniature transducer.

(i) **Tilt** Following supine control measurements, patients were tilted rapidly to 60° and were maintained in this position for 15 min. From recording continued throughout the study, results were analysed of data sampled at 1, 5, 10 and 15 min.

(ii) **Valsalva manoeuvre** This was performed by the patient blowing through a mouthpiece into an Accoson mercury sphygmomanometer for 15 s, producing a pressure of 30 mm Hg throughout this time. The manoeuvre was assessed by the degree of facial plethora and the state of the patient's neck veins. A characteristic gasp on release at the end of 15 s confirmed a satisfactory procedure. The usual four phases were recognised. In addition, phase II was divided into IIa (the lowest pressure at the first part of phase II) and IIb (the peak of the rise occurring at the end of phase II). Mean blood pressure and R–R interval were measured during each phase of three separate Valsalva manoeuvres, and the three sets of data were then averaged on each occasion. The Valsalva ratio (the longest R–R interval in Phase IV divided by the shortest R–R interval during the procedure) also was measured on each occasion.

(iii) **Handgrip** The response to handgrip was measured as the maximum increase in blood pressure and heart rate after 3 min of squeezing a calibrated handgrip dynamometer with the dominant hand at 30% of maximum voluntary contraction.

**Sino-aortic baroreflex sensitivity**

Baroreflex activity was measured using the injection of bolus doses of phenylephrine to produce a rise in systolic pressure of approximately 20 mm Hg and a concomitant reflex bradycardia (Smyth et al., 1969). A linear relationship is observed when pulse interval is plotted against systolic blood pressure and analysed beat by beat after exclusion of inspiratory beats. The slope of the regression line of pulse interval on systolic blood pressure is a measure of the sensitivity of the sino-aortic baroreflex. The set point of this reflex is determined from resting values of blood pressure and the corresponding pulse interval before injection of phenylephrine.

**Protocol**

Patients were admitted to an open ward and allowed to acclimatise. Arterial cannulation was performed early the next morning, and the line was connected to the Grass recorder. After an hour's acclimatisation, the reflex tests were performed. Following these, the arterial line was connected to the ambulatory blood pressure equipment. A diary card was then provided, and the subject was told to be active within the confines of the hospital grounds.

Patients received 30 mg of nicardipine orally at 08.00 h the following morning. At 09.00 h the arterial cannula was reconnected to the Grass recorder, and the protocol was repeated as above. Patients were allowed home at 18.00 h after the single dose and then were treated for 2 months with oral nicardipine 20, 30, or 40 mg at 08.00, 14.00 and 20.00 h. The dose was titrated in the Hypertension Clinic, and a fall in mean cuff pressure of 10% was regarded as a satisfactory response. After 2 months of outpatient treatment the patients were readmitted, and the measurements were repeated following the same protocol described above.

**Statistics**

Results were expressed as mean ± s.d. The significance of the differences between the mean values was analysed by Student's *t*-test, at the 5% level.

**Results**

**Casual blood pressure**

The mean casual blood pressure on admission was 171/103 ± 27/19 mm Hg: after treatment for 2 months this fell to 145/95 ± 17/14 mm Hg (*P* = 0.01 for systolic blood pressure and *P* < 0.05 for diastolic blood pressure).
**Figure 1** Blood pressure and heart rate observations before and after single-dose and multiple-dose nicardipine therapy. The resting (□) maximum levels of blood pressure were lower after nicardipine therapy, but there was no significant alteration in the change in pressure and heart rate with respect to tilt for 15 min at 60° (■).

**Intra-arterial blood pressure**

After treatment for 2 months the 24 h mean intra-arterial blood pressure fell from 161/102 ± 9/13 to 147/93 ± 70/12 mm Hg (P < 0.05); during the waking period mean intra-arterial blood pressure fell from 165/105 ± 6/12 to 150/96 ± 14/12 mm Hg (P < 0.05). Mean systolic variability did not change during the waking period (17 ± 2 control vs. 17 ± 4 mm Hg) and diastolic variability similarly remained unaltered (12 ± 2 control vs 13 ± 2 mm Hg).

**Heart rate**

There was no significant difference in heart rate after chronic nicardipine therapy (84 ± 12 control vs 80 ± 9 beats min⁻¹).

**Cardiovascular reflexes**

(i) **Tilt** Compared with pretreatment control, systolic and diastolic blood pressure were lower in the supine position and at 60° tilt after both the single and multiple doses of nicardipine (Figure 1). There was no evidence of postural hypotension.

(ii) **Valsalva manoeuvre** After the single and multiple doses the mean arterial pressure was reduced significantly during all phases (Figure 2). Heart rate was significantly increased during all phases following the single dose but was slower than control values in all phases after multiple-dose treatment, though this did not achieve statistical significance. The Valsalva ratio remained unchanged (ratio 1.5 ± 0.2 control vs 1.4 ± 0.1 single dose vs 1.5 ± 0.1 multiple dose).

(iii) **Handgrip exercise** Resting and maximal systolic blood pressure were reduced significantly in the single-dose study; after multiple doses,
The magnitude heart rate to control levels indicating downwards, point of the reflex during maximal systolic blood fall significant in increase) different significantly mean the (iv) Sino-aortic group treatment (1984).

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Table 1 Intra-arterial blood pressure and heart rate changes before and after 3 min handgrip exercise (% increase)

Figure 3 Baroreflex set points during control, single-dose and multiple-dose studies. Mean values ± s.e. mean are plotted. After multiple-dose therapy, the set point of the reflex and the whole curve shifted to the left. Modified from Young et al. (1984).

maximal systolic blood pressure was reduced, but not significantly. After the single dose, mean heart rate was increased significantly but returned to control levels after multiple-dose treatment. The magnitude of the pressor response was not significantly different from control in either treatment group (Table 1).

(iv) Sino-aortic baroreflex sensitivity A plot of the mean values of the slopes for all measurements made during the control and treatment periods is shown in Figure 3. After a single dose, the set point of the reflex moved to the left, indicating a significant fall in mean systolic pressure, and downwards, indicating a significant increase in heart rate (reduction in pulse interval) ($t = 2.53, P < 0.05$). This acute response to the drug demonstrates deactivation of the baroreflex mechanism (a tachycardia in response to the acute fall in blood pressure). However, the set point of the baroreflex was quite different after chronic treatment. There was a continuing shift of the set point to the left, i.e. a persisting fall in blood pressure, but the mean HR returned to control values ($t = 0.63, P = NS$), indicating that resetting of the baroreflex mechanisms occurred in order to buffer pressure at a lower level.

Side effects

After the single dose of nicardipine, one patient complained of facial flushing and headache, which subsided after 2 h. During the 2 month treatment period, one patient complained of headache necessitating reduction of the dose from 30 to 20 mg three times daily, and two patients complained of urinary frequency. No patient complained of fluid retention, and mean body weight did not change during this study (71 ± 10 control vs 70 ± 9 kg).

Discussion

Our results indicate that single and multiple doses of nicardipine significantly lower blood pressure, although blood pressure variability was not significantly affected. This confirms previous reports of the hypotensive effects of calcium antagonists (McLeay et al., 1983). A highly significant finding was that although the baroreflex mechanism was deactivated following the single oral dose (tachycardia occurring in response to the acute fall in blood pressure), after treatment for 2 months the heart rate was not different from the control levels despite the persisting fall in blood pressure, indicating that the baroreflex arc had been reset. The acute tachycardia and chronic resetting of the baroreflex arc also were seen throughout the other reflex tests. In each test the drug produced similar effects, namely a reduction of blood pressure after both single and multiple doses coupled with a tachycardia after the single dose but a return of the heart rate to control value after long-term therapy.

There was a fall in blood pressure after nicardipine. However, the percentage increase in pressure after tilting, Valsalva's manoeuvre, and handgrip was not significantly different from that observed with no therapy. Thus, nicardipine did
not significantly alter the vasopressor effects. These observations are in keeping with the failure of nicardipine to reduce blood pressure variability over prolonged periods.

Our observations on baroreflex activity and reflex cardiac control confirm our previous experience with nifedipine (McLeay et al., 1983) and, furthermore, show that resetting already has occurred by 8 weeks. This study does not explain the precise mechanism responsible for resetting. However, resetting could be caused by changes in the sino-aortic baroreceptors themselves, changes at the sino-atrial node, or centrally. Our observations suggest that in hypertensive man nicardipine and nifedipine have little, if any, direct negative chronotropic effect at the sino-atrial node. Direct recording of carotid sinus discharge frequency in isolated carotid sinuses of experimental animals suggest that over the course of a few days the baroreceptors adapt to acute changes in blood pressure, with discharge frequency rapidly returning towards control levels (Sleight et al., 1977). We favour baroreceptor adaptation as the mechanism responsible for baroreflex resetting in our hypertensive patients.

In contrast to our study using nifedipine, nicardipine did not cause an increase in baroreflex sensitivity, suggesting that facilitation of baroreflex buffering or arterial pressure changes is not essential for the hypotensive effects of calcium channel antagonists.

We conclude that nicardipine is useful as monotherapy in the treatment of mild to moderate hypertension. Simultaneous treatment with beta blockers to reduce heart rate, although often recommended, is not necessary as the baroreflex arc resets during long-term treatment. Furthermore, the absence of fluid retention and weight gain may give this type of calcium channel blocker an advantage over other vasodilators in the management of essential hypertension.

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References


