SHORT COMMUNICATION

Baroreflex setting and sensitivity after acute and chronic nicardipine therapy

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Summary
1. Intra-arterial pressure, baroreflex sensitivity and the baroreflex set point were measured in eight patients with essential hypertension during a control period and then after acute treatment (2 h after a 30 mg oral dose) and after chronic treatment (at least 2 months) with nicardipine hydrochloride, a calcium channel antagonist.

2. Mean intra-arterial blood pressure fell after the acute treatment from 130 ± 14 (SD) control to 118 ± 11 mmHg, \( P < 0.05 \), and after chronic treatment to 112 ± 19 mmHg, \( P < 0.05 \). Heart rate increased from 72 ± 11 control to 81 ± 16 beats/min, \( P < 0.05 \), during acute treatment indicating activation of the baroreflex control mechanism, but returned to control values with chronic treatment (72 ± 11 control vs 69 ± 9 beats/min chronic), indicating a significant shift to the left of the baroreflex set point. There was no change in baroreflex sensitivity after either acute or chronic treatment (control 4.7, acute 4.3, chronic 5.1 ms/mmHg, \( P \) not significant for all values).

3. Nicardipine significantly reduces mean intra-arterial pressure both acutely and chronically; the latter is associated with a return of the heart rate to control values due to resetting of the baroreflex control mechanism.

Key words: calcium channel antagonists, nicardipine, pressoreceptors.

Introduction
Previous studies have shown the efficacy of calcium channel antagonists for treatment in hypertension, and their use as primary monotherapy has been advocated [1-3]. All studies of these drugs show a significant hypotensive effect, but the reported changes in the heart rates of patients on chronic treatment have been conflicting [1, 3]. We have studied the changes in heart rate and blood pressure during acute and chronic treatment with a new calcium channel antagonist, nicardipine hydrochloride, both acutely and chronically. Nicardipine hydrochloride is similar in structure and action to nifedipine, which has no known effects on sino-atrial or atrio-ventricular nodes or on the myocardium.

Patients and methods
We studied eight patients with essential hypertension with no evidence of target organ damage. Essential hypertension was defined as a casual blood pressure on three separate occasions in outpatients of 140/90 mmHg or greater after 5 min rest supine (phase V diastolic). Target organ damage was defined as clinical evidence of ischaemic heart disease or cerebrovascular disease, left ventricular hypertrophy, renal impairment or accelerated hypertension. Secondary hypertension was excluded by clinical examination, measurement of plasma electrolytes and creatinine and intravenous pyelography. None of the patients had received therapy for at least 2 weeks before study. Five patients were male and the age range of the group was 36-64 years, mean 49 years. The
average outpatient cuff pressures (mmHg) were 180 ± 27 systolic, 110 ± 12 diastolic and 133 ± 17 mmHg mean, measured with a standard mercury sphygmomanometer. After admission, the cuff pressure was measured after 15 min supine rest with a Hawksley random zero sphygmomanometer.

Intra-arterial pressure was measured from the patient’s non-dominant brachial artery via a 1 mm diameter Teflon cannula, which in turn was connected via a three-way tap and transducer to a Grass polygraph physiological recorder. Heart rate was recorded simultaneously on the same chart.

After arterial cannulation each patient rested for 30 min. Heart rate and intra-arterial blood pressure were measured over the 30 s before each injection of phenylephrine. Three such measurements of heart rate and intra-arterial pressure were averaged and taken as the set point of the baroreflex. Baroreflex activity was then measured, using the method of Smyth et al. [4], by injection of bolus doses of phenylephrine to produce a rise in systolic pressure of 20 mmHg and a bradycardia via the sino-aortic baroreflex mechanism. The slope of the regression line of pulse interval on systolic blood pressure was taken as the baroreflex sensitivity. In each patient phenylephrine injections were repeated until at least three had produced satisfactory rises in systolic pressure. The average of the slopes of the three statistically most significant \(P < 0.05\) regression lines was calculated for each patient and taken as the baroreflex sensitivity.

The procedure was repeated the next morning 2 h after an oral dose of nicardipine hydrochloride (30 mg). Patients were then treated for at least 2 months with oral nicardipine 20, 30 or 40 mg thrice daily (08.00, 14.00 and 20.00 hours), the dose depending on the patient's blood pressure response. After the chronic therapy patients were re-admitted to hospital and the measurements of intra-arterial pressure and baroreflex sensitivity were repeated.

Plasma volume was also measured during control and chronic observation, by the use of \(^{125}\)I-labelled human albumin and a dilution assay.

Patients gave informed consent and the study was approved by the Hospital Ethics Committee. Results were analysed by using Student’s paired t-test.

**Results**

Mean intra-arterial blood pressure fell during the acute period from 130 ± 14 (SD) control to 118 ± 11 mmHg, \(t = 3.0, P = 0.02\). This acute fall in pressure was associated with a significant increase in heart rate from 72 ± 11 to 81 ± 16 beats/min, \(t = 2.53, P < 0.05\). After chronic therapy the mean intra-arterial blood pressure remained significantly reduced at 112 ± 19 mmHg \((r = 2.50, P < 0.05)\), but there was no significant change in heart rate from control values \((72 ± 11\) control vs 69 ± 9 beats/min chronic, \(t = 0.63, P = \text{N.S.}\)).

Mean systolic intra-arterial pressure fell from 184 ± 14 to 167 ± 14 mmHg after acute treatment \((t = 2.79, P < 0.05)\) and to 160 ± 25 mmHg \((t = 2.55, P < 0.05)\) after chronic treatment. Baroreflex sensitivity was not significantly changed after either the acute or chronic treatment \((\text{control} 4.7, \text{acute} 4.3, \text{chronic} \ 5.1\ ms/mmHg; t = 0.74, 0.50 and 1.1 \text{respectively}; P = \text{N.S. for all values})\).

Fig. 1 shows that after acute treatment the set point of the reflex moves to the left, indicating a significant fall in mean systolic pressure, and downwards, indicating a significant \((t = 2.53, P < 0.05)\) increase in heart rate (reduction in pulse interval). This acute response to the drug demonstrates an activation of the baroreflex control mechanism. The set point of the baroreflex, however, is quite different after chronic treatment; there is a continuing shift of the set point to the left, i.e. a persisting significant fall in mean systolic pressure, but the heart rates have now returned to control values \((t = 0.63, P = \text{N.S.})\). This indicates that resetting of the baroreflex mechanism has occurred in order to buffer pressure at a lower level.
Baroreflexes and nicardipine therapy

The cuff blood pressure fell from 171/103 ± 27/19 to 149/95 ± 17/14 mmHg during chronic treatment (t = 3.5, P = 0.01 for systolic and t = 2.8, P < 0.05 for diastolic). Plasma volume did not alter after chronic therapy (39 ± 4 control vs 38 ± 6 ml/kg chronic, t = 0.56, P = N.S.), and nor did weight (71 ± 10 control vs 70 ± 9 kg chronic).

Discussion

Our results indicate that nicardipine significantly lowers blood pressure both acutely and chronically. This confirms previous reports of the hypotensive effects of calcium antagonists [1-3, 5]. The heart rate changes seen during treatment with nicardipine can be explained by an acute activation of the baroreflex control mechanism with a resetting of the reflex after chronic therapy; the latter confirms our previous experience with nifedipine [3]. Similar changes in the opposite direction occur in response to acute hypertension, when there is an initial bradycardia followed by a gradual return of the heart rate towards normal. From experimental studies in dogs and rats [6-8] it appears that resetting of baroreflexes occurs over a period of a few days in response to acute hypotension or hypertension. The precise mechanism responsible for resetting cannot be elucidated from this study; however, resetting could be due to changes in the sino-aortic baroreceptors themselves, or changes at the sino-atrial node or centrally. Our observations suggest that both nicardipine and nifedipine have little, if any, direct negative chronotropic effect at the sino-atrial node in hypertensive man. Direct recording of carotid sinus nerve discharge frequency in isolated carotid sinuses of experimental animals suggests that the baroreceptors show adaptation occurring over the course of a few days [7, 9] in response to acute changes in blood pressure, with discharge frequency returning rapidly towards control. We favour baroreceptor adaptation as the mechanism responsible for baroreflex resetting in our hypertensive patients. Other drugs such as captopril produce profound acute falls in blood pressure without changes in heart rate, and hydralazine is said to cause a chronically sustained tachycardia. These responses may reflect various drug actions at different sites of the reflex arc.

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

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References