Effects of nicardipine on aldosterone release and pressor mechanisms

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- 1 This study evaluated the effects of nicardipine, following intravenous infusion and oral administration, on the pressor and aldosterone responses to infused angiotensin II.
- 2 Six healthy, normotensive male subjects were studied.
- 3 Following administration of nicardipine, no significant change in blood pressure was seen.
- 4 Nicardipine attenuated the pressor response produced by intravenous administration of angiotensin.
- 5 Nicardipine did not inhibit the aldosterone response to angiotensin.

Keywords aldosterone angiotensin nicardipine

Introduction

The role of calcium ions in hormone release was first described by Douglas and co-workers (Douglas & Rubin, 1963; Douglas & Poisner, 1964). In particular, there is evidence that adrenal steroidogenesis is calcium dependent (Farese & Prudente, 1978) and that the aldosterone response to angiotensin II is associated with the intracellular accumulation of calcium (Shima *et al.*, 1979; Fakunding & Cati, 1980).

In human studies, however, evidence that calcium antagonists significantly interfere with hormone release is not clearly established. However, there is evidence that nifedipine acutely diminished the aldosterone response to angiotensin II (Millar *et al.*, 1981; Vierhapper & Waldhausl, 1982). This inhibition was not sustained during chronic therapy (Bianchetti *et al.*, 1982; Millar *et al.*, 1983).

This report briefly describes the effects of acute and chronic dosing with a dihydropyridine derivative, nicardipine, on the pressor and aldosterone responses to infused angiotensin II in healthy male volunteers. The full details of this investigation are described elsewhere (Pasanisi *et al.*, 1985a).

Methods

Six healthy normotensive males (23–26 years; 63–80 kg) gave written informed consent to participate in the clinical trial.

The study, approved by the Hospital Research and Ethics Committee, was a random order, double-blind, cross-over comparison of three treatments:

1. Placebo,
2. Acute, intravenous nicardipine (by infusion at 5 mg h⁻¹ for 2.5 h),
3. Steady-state oral nicardipine (after 1 week's therapy with 30 mg three times daily).

To maintain the double-blind design, subjects were studied during three phases, each of 1 week duration and culminating in a final study day when intravenous therapy was added.

On the final day of each treatment phase, subjects reported to the Clinical Pharmacology Research Unit where they rested supinely for 6 h. An intravenous cannula was inserted into each forearm, and a blood pressure cuff was attached. After not less than 20 min of supine rest, the intravenous infusion of nicardipine 5 mg h⁻¹, or an equivalent volume of 0.9% sodium chloride

solution, was started for a run of 2.5 h. One hour later, through the cannula in the opposite arm, an intravenous infusion of angiotensin II was started for a run of 1.5 h with fixed incremental doses of 5, 10, and 20 ng kg⁻¹ min⁻¹, each administered for 30 min.

Supine blood pressure and heart rate recordings, by semi-automated sphygmomanometer (Sentron) and radial pulse counts, were made at frequent intervals, in particular at 5, 10, 20, and 30 min during each infusion dose. Venous blood samples were withdrawn at times 0, 1 h (i.e. pre-angiotensin) and at 1.5, 2.0, and 2.5 h (corresponding to the end of each of the three angiotensin dose levels) for subsequent measurements of:

1. Plasma aldosterone (de Man *et al.*, 1980),
2. Plasma renin activity (Derkx *et al.*, 1976),
3. Plasma noradrenaline (Henry *et al.*, 1975),
4. Plasma cortisol and ACTH (radioimmunoassay).

Statistical analysis

Analysis of variance was used for the repeated measurements, and the results are presented as mean values $\pm$ s.d. Statistical significance is taken at the 5% level, $P < 0.05$.

Results

Blood pressure and heart rate

There were no significant changes in blood pressure associated with 1 week of therapy with oral nicardipine. The introduction of the first dose of 30 mg was associated with a transient increase in standing heart rate at 2 h – 83 ± 11 beats min⁻¹ compared with 72 ± 12 beats min⁻¹ after placebo.

Pressor responses to angiotensin II

The mean blood pressure responses to the incremental infusion of angiotensin II are shown in Figure 1. Compared with the increase after placebo, there was a significantly smaller increase in mean arterial pressure following both intravenous and oral nicardipine. Following a dose of 5 ng kg⁻¹ min⁻¹, the increase in MAP was 9.1 ± 5.5 with placebo, compared with 4.7 ± 4.0 with intravenous and 4.8 ± 5.5 mm Hg with oral nicardipine. The corresponding increases after the 10 ng kg⁻¹ min⁻¹ dose were 16.7 ± 7.6 ,

Figure 1 Pressor and aldosterone responses (mean $\pm$ s.d.) to angiotensin II, after placebo (x), oral nicardipine (○) and intravenous nicardipine (●). The pressor response is shown as the increase from baseline of mean arterial pressure.

10.4 ± 6.1 , and 10.5 ± 6.0 ; after the 20 ng kg⁻¹ min⁻¹ dose, the corresponding increases were 23.6 ± 9.5 , 13.4 ± 6.7 , and 16.5 ± 7.3 mm Hg.

Aldosterone responses to angiotensin II

These data are shown in Figure 1. After 1 week of treatment with oral nicardipine the mean plasma aldosterone level (48 ± 20 pg ml⁻¹) was not significantly different from the mean level (44 ± 13 pg ml⁻¹) after placebo. Responses to infused angiotensin showed wide inter-individual variations. There were, however, no significant differences attributable to nicardipine in the patterns of response, a similar increase in plasma aldosterone concentration being obtained with all three treatments. At the highest dose of the angiotensin infusion (20 ng kg⁻¹ min⁻¹), the aldosterone levels (pg ml⁻¹) were 85 ± 16 after placebo, compared with 73 ± 18 after intravenous nicardipine infusion, and 101 ± 16 after oral nicardipine.

Table 1 Mean values of plasma renin activity, plasma noradrenaline and plasma cortisol after different doses of angiotensin

		Angiotensin infusion ($\text{ng kg}^{-1} \text{ min}^{-1}$)			
	Baseline	0	5	10	20
	<i>Plasma renin activity (normal range: 4–12 ng AI ml⁻¹ h⁻¹)</i>				
Placebo	1.2±0.8	1.0±0.5	0.5±0.3	0.3±0.1	0.4±0.2
Intravenous nicardipine	1.5±1.0	2.9±1.8	1.1±0.6	0.7±0.4	0.8±0.3
Oral nicardipine	2.6±1.5	3.0±1.5	1.7±1.0	1.0±0.5	0.8±0.4
	<i>Plasma noradrenaline (normal range: 0–7 nmol l⁻¹)</i>				
Placebo	1.6±0.4	1.9±0.6	1.4±0.5	1.4±0.7	1.7±0.6
Intravenous nicardipine	2.3±1.3	2.7±1.0	2.7±1.7	2.7±1.2	2.6±1.0
Oral nicardipine	1.6±0.3	2.2±0.6	2.4±0.5	2.2±0.7	2.3±1.5
	<i>Plasma cortisol (normal range: (08.00 h): 330–770 nmol l⁻¹)</i>				
Placebo	567±157	340±98	303±68	257±65	242±52
Intravenous nicardipine	513±137	343±96	303±99	293±103	332±135
Oral nicardipine	428*±93	345±78	332±92	302±105	308±115

* $P < 0.05$.*Plasma renin activity, noradrenaline, cortisol and ACTH*

These data are summarised in Table 1. During the infusion of angiotensin II there were no significant differences associated with the oral or intravenous administration of nicardipine. Only the baseline (0 time) cortisol concentrations after one week of treatment with oral nicardipine were significantly different from placebo. The corresponding ACTH levels (pg ml^{-1}) were not significantly different: 12.8 ± 4.9 after oral nicardipine compared with 16.7 ± 10.9 after intravenous nicardipine and 14.8 ± 4.3 after placebo.

Discussion

In this group of young normotensive subjects, administration of nicardipine was not associated with any significant reduction in blood pressure, either following i.v. infusion or after oral therapy for 1 week. However, a transient, slight increase in standing heart rate, observed 2 h after the first oral dose, was early evidence of a haemodynamic effect.

The intravenous administration of angiotensin II caused the expected dose-related increase in blood pressure (Bean *et al.*, 1979). However, the

pressor response to angiotensin was significantly and substantially attenuated by both intravenous and oral administration of nicardipine. Although the expected increase in blood pressure was achieved in all subjects during placebo administration, the increase in some subjects was very slight during nicardipine treatment. A similar reduction in pressor responsiveness to angiotensin has been reported for other calcium antagonists, including nifedipine (Millar *et al.*, 1983) and verapamil (Pasanisi *et al.*, 1985b).

Nicardipine did not inhibit the aldosterone response to angiotensin II. It has been suggested that inhibition of aldosterone production may be an important component of the antihypertensive effect of calcium antagonists (Millar *et al.*, 1981), and there is evidence that nifedipine inhibits the aldosterone response (Millar *et al.*, 1981; Vierhapper & Waldhausl, 1982). In this study, the intravenous infusion of nicardipine did not interfere with the aldosterone response. There is no conclusive evidence that long-term therapy with nifedipine inhibits the aldosterone response (Bianchetti *et al.*, 1982; Millar *et al.*, 1983); similarly, in this study, therapy with nicardipine for 1 week had no significant effect on the aldosterone response. It has been shown that aldosterone levels were low relative to the level of plasma renin activity during chronic therapy with

nifedipine (Hiramatsu *et al.*, 1982), but this was not confirmed in the present study with nicardipine.

Of the other hormones measured, only the baseline concentration of cortisol was significantly different in association with oral nicardipine. It is unlikely that this difference had any clinical relevance as there was no significant difference in ACTH and no difference in the other cortisol levels during the angiotensin infusion. Previous studies with nifedipine have shown no effect on cortisol production (Millar *et al.*, 1982).

In conclusion, this study provides no evidence that inhibition of aldosterone release contributes to the antihypertensive action of nicardipine after either intravenous infusion or oral administration.

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