Influence of nicardipine on blood pressure, renal function and plasma aldosterone in normotensive volunteers

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1 The influence of the calcium antagonist nicardipine on intrarenal sodium handling and angiotensin II induced secretion of aldosterone was investigated in 18 normotensive volunteers after the first dose and after 1 week of treatment (20 mg three times daily).

2 A short-lasting natriuresis was observed, which was caused by a decreased reabsorption of sodium localised in both proximal and distal tubules.

3 Log plasma renin activity (PRA) fell significantly on each day during angiotensin II infusion, while log plasma aldosterone (PA) rose significantly.

4 The log PRA/log PA ratio was increased during nicardipine treatment. The secretion of aldosterone, induced by angiotensin II, was not influenced by nicardipine treatment. No effect of the drug on adrenal responsiveness to angiotensin II was found.

Keywords aldosterone angiotensin II intrarenal sodium handling nicardipine

Introduction

Calcium antagonists cause a systemic vasodilatation by inhibiting calcium-induced contraction of smooth muscle (Fleckenstein, 1977). Nicardipine is a dihydropyridine compound structurally related to nifedipine and has been shown to have a diuretic effect in dogs (Abe *et al.*, 1983). This effect also has been reported for nifedipine in humans (Yokoyama & Kaburagi, 1981). In addition, nifedipine has been reported to inhibit the aldosterone response to angiotensin II (Millar *et al.*, 1981; Vierhapper & Waldhäusl, 1982).

The efficiency of nicardipine as an antihypertensive agent also may be related to this natriuretic effect. The present study was designed with a twofold aim: first, to investigate the natriuretic effect of nicardipine (Study I) and second, to evaluate the aldosterone response to angiotensin II during nicardipine medication (Study II).

The results from Study I have been published (van Schaik *et al.*, 1984). Some of these data are included in this paper because they are relevant to both the methods of Studies I and II and to the interpretation of the aldosterone response following treatment with nicardipine.

Methods

Study I

The influence of nicardipine on renal function was studied in ten normotensive healthy male volunteers, aged 21-34 years. Informed consent was given by all the subjects, and the protocol was approved by the Hospital Ethics Committee.

During two consecutive weeks, the volunteers took one capsule three times daily (at 09.00, 14.00, and 20.00 h), at least 1 h after their meals. The capsules contained placebo during the first week, and 20 mg nicardipine during the second week. A capsule count was performed to check compliance. The subjects had a free diet, and they were instructed to avoid changes in their eating habits. On the last day of the placebo period and on the first and last day of nicardipine treatment they took their morning capsule at 09.00 h and then rested in the supine position. At 11.00 h blood was taken for measurement of supine plasma renin activity (PRA), plasma aldosterone (PA), serum creatinine, sodium and potassium. At 11.30 h blood pressure was measured by Arteriosonde®, and the average of five readings was calculated. The subjects consumed a light

lunch at noon. From 13.00 till 14.00 h the individuals were given a waterload of 25 ml kg⁻¹. During the following hours the waterload was maintained by drinking a volume of water equal to the diuresis. At 14.00 h they took their second capsule. After 15.00 h urine was collected every 20 min and, when the urine osmolality was below 80 mosmol kg⁻¹, three consecutive 20 min urine portions were sampled. Blood was taken in the middle of each 20 min period.

Study II

The influence of nicardipine on the angiotensin II induced secretion of aldosterone was examined in eight normotensive healthy male volunteers (aged 19–24 years). The medication schedule was the same as described above. This study was performed in a metabolic unit to ensure that the subject's diet contained 200 mmol sodium and 80 mmol potassium.

On the last day of placebo and on the first and last days of nicardipine treatment, the subjects arrived at the hospital at 08.30 h, and rested in the supine position, and were given the dose of nicardipine. Four individuals received their medication orally and four intravenously (4 mg) on the two nicardipine study days; on the other days, all medication was taken orally. A 30 min control period preceded each experimental infusion. Angiotensin II (A II) (Hypertensin®, Ciba) was diluted in 5% glucose solution, infused at rates of 1.0 and 3.0 ng kg⁻¹ min⁻¹, each for 0.5, and at 10.0 ng kg⁻¹ min⁻¹ for 1 h. At the end of each A II infusion period, blood pressure was measured, and an average of three measurements was calculated. Before administration of the morning dose, blood was sampled for measurement of supine PRA, PA, noradrenaline (NA), and adrenaline (Ad). After the second period of A II infusion, blood was sampled for PA and after the third period of A II infusion blood for PRA, PA, NA, and Ad.

Mean arterial pressure (MAP) was computed as one third of the systolic pressure plus two-thirds of the diastolic pressure. PRA was determined radio immunologically, according to a modification of the method described by Haber *et al.* (1969). Undiluted plasma was incubated for 1 h at 37°C and pH 5.6 in the presence of phenylmethylsulfonyl fluoride and 8-hydroxy-quinoline, deproteinized with 3 volumes of a 9:1 mix of acetone/4 N ammonia 9:1, dried under air stream, and dissolved in PRA buffer. PA was assessed by a nonchromatographic direct radio-

immunoassay after extraction from 2 ml plasma with dichloromethane (Boer *et al.*, 1983). NA and Ad were measured by a radio-enzymatic technique (Peuler & Johnson, 1977). Plasma and urine were analysed for osmolality, serum creatinine, sodium and potassium, according to standard hospital procedures. Clearances were calculated according to standard formulas. The following parameters were calculated for an estimation of proximal and distal sodium reabsorption per glomerular filtration rate (GFR):

$$\begin{aligned} fC_{H_2O} &= \text{fractional maximal free water} \\ &\text{clearance} \\ &= \frac{(Uv \max - C_{osm})}{GFR} \times 100 (\%) \end{aligned}$$

$$\begin{aligned} fPR_{Na} &= \text{fractional proximal reabsorption} \\ &\text{of sodium} \\ &= 100 - \left\{ \frac{(U[Na + K] \cdot Uv \max)}{F_{Na}} \cdot 100 + fC_{H_2O} \right\} (\%) \end{aligned}$$

$$\begin{aligned} fDR_{Na} &= \text{fractional distal sodium} \\ &\text{reabsorption} \\ &= \frac{(Uv \max - C_{osm})}{(U[Na + K] \cdot Uv \max) / P_{Na}} \times 100 (\%) \end{aligned}$$

where

C_{osm} = osmolar clearance (ml min⁻¹),

u_{Na+K} = sum of urinary concentrations of sodium and potassium (mmol l⁻¹),

F_{Na} = filtered sodium (mmol l⁻¹),

P_{Na} = plasma concentration of sodium (mmol l⁻¹),

$Uv \max$ = maximal diuresis during waterload (ml min⁻¹).

Statistical evaluation

Values are expressed as means $\pm$ s.e. mean. Differences between placebo and the first and the last days of nicardipine therapy were evaluated by the Student's *t*-test for paired data. Difference in the A II-induced secretion of aldosterone before and during nicardipine treatment was calculated by two-way analysis of variance with unequal proportional subclass sizes (ANOVA).

Results

Measurements obtained in all 18 patients

The effects of nicardipine on the variables measured are shown in Table 1. The means of

Table 1 Effects of nicardipine ($n = 18$)

	<i>Last day placebo</i>	<i>First day nicardipine</i>	<i>Last day nicardipine</i>
Body weight (kg)	74.4 ± 2.0	—	74.2 ± 1.8
MAP (mm Hg)	85 ± 3	83 ± 3	82 ± 3*
Heart rate (beats min ⁻¹)	57 ± 4	57 ± 3	57 ± 3
log PRA (fmol l ⁻¹ s ⁻¹)	2.43 ± 0.07	2.49 ± 0.06	2.57 ± 0.07*
log PA (pmol l ⁻¹)	2.36 ± 0.06	2.25 ± 0.05	2.30 ± 0.06
log PRA/log PA	1.04 ± 0.02	1.11 ± 0.03*	1.13 ± 0.03*

All values obtained 2 h after oral medication of placebo or 20 mg nicardipine both given three times daily during the week.

MAP = mean arterial pressure. PRA = plasma renin activity. PA = plasma aldosterone concentration.

* $P < 0.05$, compared with placebo values.

Table 2 Intrarenal effects of nicardipine ($n = 10$)

	<i>Last day placebo</i>	<i>First day nicardipine</i>	<i>Last day nicardipine</i>
Uv max (ml min ⁻¹)	18.1 ± 1.3	23.4 ± 1.6*	24.6 ± 1.2**
fC _{Na} (%)	1.0 ± 0.1	2.1 ± 0.1*	2.6 ± 0.0**
fC _{H₂O} (%)	11.0 ± 0.9	12.5 ± 0.7*	13.9 ± 0.8*
GFR (ml min ⁻¹)	136 ± 18	143 ± 19	137 ± 18
fPR _{Na} (%)	87.6 ± 0.8	84.9 ± 0.9*	83.2 ± 0.8**
fDR _{Na} (%)	89.1 ± 1.0	83.2 ± 1.9*	82.4 ± 1.4*

All values obtained 2 h after oral medication of either placebo or 20 mg nicardipine, each three times daily during the week.

fC_{Na} = fractional clearance of sodium. fC_{H₂O} = fractional clearance of free water. GFR = glomerular filtration rate.

fPR_{Na} = fractional proximal reabsorption of sodium. fDR_{Na} = fractional distal reabsorption of sodium.

* $P < 0.05$, ** $P < 0.01$, compared with placebo values.

bodyweight, MAP, log PRA, and log PA were calculated from the data of both studies. Bodyweight was only slightly decreased after 1 week of treatment. There was a slight decrease in blood pressure, the average fall in MAP compared with placebo being 2% after the first dose and 4% after 1 week of treatment ($P < 0.05$). Log PRA increased after 1 week ($P < 0.05$), while log PA decreased somewhat. Accordingly, log PRA/log PA was found to be higher during nicardipine treatment compared with placebo ($P < 0.05$).

Study I intrarenal sodium handling during waterloading (n = 10)

In Table 2 are shown the effects on a number of intrarenal measurements before and during nicardipine administration.

Maximal diuresis was increased after the first dose ($P < 0.05$) as well as after 1 week of

nicardipine treatment ($P < 0.01$). Creatinine clearance measured during waterloading remained unchanged throughout nicardipine treatment in comparison with the placebo period. A significant increase of fractional sodium clearance was present during nicardipine treatment ($P < 0.05$). The fractional proximal reabsorption of sodium (fPR_{Na}) fell significantly both after the first dose ($P < 0.05$) and after 1 week treatment ($P < 0.01$). The fractional distal reabsorption of sodium (fDR_{Na}) also was found to be significantly lower on both treatment study occasions ($P < 0.05$) (Figure 1).

Study II angiotensin II infusions (n = 8)

The effects of A II on a number of haemodynamic and hormonal values before and during nicardipine treatment are shown in Table 3. MAP increased on each occasion during A II infusion. Log PRA fell significantly on each day during

Figure 1 Fractional proximal (□) and distal (▨) reabsorption of sodium. * Significant difference from placebo $P < 0.05$, ** significant difference from placebo $P < 0.01$.

A II infusion, while log PA rose significantly. NA and Ad increased slightly. These effects following A II infusion were consistent after single doses and chronic treatment with nicardipine.

Adverse reactions

One volunteer complained of tiredness and one showed flushing during nicardipine treatment, but neither of them requested to be withdrawn from the study.

Discussion

Nicardipine is a calcium antagonist, structurally related to nifedipine. The antihypertensive effect of nicardipine has been documented previously (Takabatake *et al.*, 1982; Jones *et al.*, 1983).

In this study of healthy volunteers we found a reduction in blood pressure of about 2% following an initial dose of nicardipine, with a further reduction to about 4% after a week. This minor fall in blood pressure seemed clinically unimportant. PRA increased significantly, while PA fell slightly after 1 week of treatment.

Some studies have reported an increase of PRA following nifedipine administration (Aoki, 1979; Olivari *et al.*, 1979; Valdes *et al.*, 1982), while others have found no significant changes (Thibonnier *et al.*, 1980; Soto *et al.*, 1981). After nifedipine treatment, PA has been reported to

remain unchanged (Hiramatsu, 1982) or decreased (Heidland *et al.*, 1982; Thibonnier *et al.*, 1980), despite an increase in PRA. This was attributed to a decrease in the sensitivity of the zona glomerulosa to A II (Millar *et al.*, 1982). Indeed, studies with isolated glomerulosa cells revealed that during the stimulation of the aldosterone secretion by A II, the entry of Ca into the cells served an important messenger function that could be blocked by the calcium antagonist verapamil (Foster *et al.*, 1981; Fakunding *et al.*, 1979).

The decrease in plasma aldosterone, caused by calcium antagonists such as nifedipine and nicardipine, in addition to their vasodilating properties, may lead to sodium loss and thereby enhance their efficiency as antihypertensive agents. Although bodyweight was not significantly decreased after 1 week of nicardipine treatment, the significant increase in PRA could indicate some volume depletion effect. The fact that there was no concurrent increase in PA, and thus a significant increase in log PRA/log PA ratio, suggests some additional inhibition of aldosterone secretion.

It has been reported that nifedipine decreased the aldosterone response to A II in healthy humans (Millar *et al.*, 1981; Vierhapper & Waldhäusl, 1982). We investigated this effect with nicardipine, but found the A II-induced increment of PA similar during placebo and nicardipine. It is possible, therefore, that nicardipine inhibits the adrenal function in some other way. More pronounced acute changes were found in renal values, especially in changes of renal sodium and water handling.

Patients treated with vasodilators, which act on resistance vessels often develop sodium retention. However, after an intravenous dose of nifedipine in humans, GFR and urinary excretion of sodium increased markedly (Klüttsch *et al.*, 1972; Yokoyama & Kaburagi, 1983; McCrorey *et al.*, 1979) found a tubular natriuretic effect, independent of GFR and renal blood flow. Previous work with acute administration of nicardipine in humans illustrated strong diuretic effects (Yokoyama & Kaburagi, 1983).

After the first dose, as well as after 1 week of treatment with nicardipine, our results showed a natriuretic effect during waterload, 2 h after administration of the drug, without a significant change in GFR. This decreased sodium reabsorption appeared to be localized to the proximal and distal tubules, although the limitations of these indirect estimations should be realised.

Table 3 Effects of nicardipine on changes induced by angiotensin II

Dose A II (ng kg ⁻¹ min ⁻¹)...	Last day placebo			First day nicardipine			Last day nicardipine					
	0.0	1.0	3.0	10.0	0.0	1.0	3.0	10.0	0.0	1.0	3.0	10.0
MAP (mm Hg) (n = 8)												
Mean	87	89	95***	107***	88	89	97**	106***	86	87	94***	101***
s.e. mean	3	2	2	3	3	2	2	2	2	2	2	3
log PRA (fmol l ⁻¹ s ⁻¹) (n = 8)												
Mean	2.26	—	—	2.01***	2.32	—	—	2.04***	2.46	—	—	2.25
s.e. mean	0.09	—	—	0.08	0.10	—	—	0.07	0.11	—	—	0.13
log PA (pmol l ⁻¹) (n = 8)												
Mean	2.21	—	2.36	2.61***	2.12	—	2.38*	2.59***	2.26	—	2.55	2.67*
s.e. mean	0.07	—	0.13	0.13	0.06	—	0.12	0.10	0.10	—	0.10	0.06
NA (nmol l ⁻¹) (n = 4)												
Mean	2.19	—	—	2.38	1.97	—	—	2.73	2.59	—	—	3.03
s.e. mean	0.73	—	—	0.44	0.51	—	—	0.84	1.12	—	—	1.05
Ad (nmol l ⁻¹) (n = 4)												
Mean	0.51	—	—	0.64	0.58	—	—	0.50	0.40	—	—	0.76
s.e. mean	0.24	—	—	0.11	0.40	—	—	0.22	0.13	—	—	0.49

P = significance of differences from the 0.0 ng kg⁻¹ min⁻¹ dose on that day.

* P < 0.05, ** P < 0.01, *** P < 0.005.

Similar intrarenal changes may not necessarily occur in patients with essential hypertension, for in such patients, we have found the GFR to be the major determinant for the increased natriuresis after nicardipine treatment (van Schaik *et al.*, 1984).

The marked difference in natriuresis during the clearance episodes on treatment with nicardipine and placebo contrasts with the negligible decrease in bodyweight and the modest increase in PRA. We therefore assume the natriuretic effect of nicardipine to be short-acting and partially compensated during 24 h with this dose and frequency of administration.

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