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Antihypertensive and renal effects of nicardipine

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Both the acute blood pressure lowering and renal effects of the calcium antagonist nicardipine and those after 1 week's treatment were investigated in 10 normotensive volunteers and in 10 patients with mild to moderate essential hypertension.

2 After 1 week of placebo, nicardipine was administered orally for 1 week (20 mg three times daily), Investigations, done on the first and last day of nicardipine treatment were compared with those on the last day of placebo.

3 During water loading, nicardipine increased urinary volume and urinary excretion of sodium significantly after 1 week nicardipine treatment.

4 In the normotensive group the natriuretic effect was caused by a decrease of fractional proximal and distal reabsorption of sodium. In the hypertensive group the natriuresis was achieved mainly by an increase of the rate of glomerular filtration (GFR) and also by a slight distal effect.

5 Our results show that nicardipine had natriuretic effects. There were trends suggesting that the renal effects may differ between patients with essential hypertension and normotensive volunteers, but the findings might also be related to differences in age between the groups.

Keywords nicardipine renal function hypertension

Introduction

Calcium antagonists are a group of chemicals, whose action is to inhibit the movement of calcium ions through the cell membrane. Nicardipine is one of this group and is structurally related to nifedipine.

Nifedipine has been shown to be a potent antagonist of calcium-induced contraction of smooth muscle (Fleckenstein, 1977), and this property induces a systemic vasodilatation and a decrease in blood pressure.

Nicardipine has been shown to have a diuretic effect in dogs (Abe *et al.*, 1983), and this effect has been reported for nifedipine in humans (Yokoyama & Kaburagi, 1981).

The objectives of this study were, firstly, to evaluate the effect of nicardipine in lowering blood pressure and secondly, to investigate the natriuretic effect of nicardipine. The demonstration of these effects in combination could point to a good therapeutic regimen in essential hypertension.

Methods

This study was performed in 10 normotensive healthy male subjects (aged 21–34 years) and in 10 hypertensive male patients (aged 24–47 years). The characteristics are shown in Table 1. All patients had uncomplicated essential hypertension and in all cases informed consent was given. The protocol was approved by the Hospital Ethical Committee. The 10 hypertensive patients were off treatment for 3 weeks preceding the study. During two consecutive weeks the individuals 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, and 20 mg nicardipine during the second week. The excess of capsules was counted afterwards to check compliance. No diet was prescribed, but they were instructed to avoid excessive alcohol intake or irregularities in their eating habits, especially the sodium intake. All subjects had the same time schedule and had their breakfast at 08.00 h. On the last day on

Table 1 Patient characteristics

Number	Age (years)	Creatinine clearance (ml/min)	Initial blood pressure (mm Hg)	Adverse reactions
(a) *Normotensive volunteers*				
1	24	133	106/60	—
2	34	136	134/88	—
3	21	151	107/60	Tiredness
4	25	158	105/62	—
5	24	131	110/62	—
6	23	128	127/70	—
7	23	146	135/64	—
8	24	158	116/66	—
9	23	125	128/83	—
10	21	98	134/74	—
(b) *Hypertensive patients*				
1	24	117	148/107	Heachache, tiredness
2	47	197	159/116	Tiredness
3	38	105	119/90	—
4	45	69	128/104	—
5	33	170	133/98	Flushing, tiredness, headache
6*	25	124	131/95	Severe flushing, headache
7	36	87	150/105	—
8	38	86	147/111	Flushing, palpitations, headache
9	30	114	139/103	Headache
10	46	186	141/93	—

Blood pressure values without therapy, measurement with Arteriosonde® after 2 h supine.
* Withdrawn from study.

placebo and both on the first and on the last day of nicardipine, they arrived at the hospital at 09.00 h, took their morning capsule and laid down. At 11.00 h blood was taken for supine plasma renin activity (PRA), plasma aldosterone (PA), creatinine, sodium, potassium and calcium. At 11.30 h blood pressure was measured by Arteriosonde® and the average of five readings was calculated. MAP was computed as one-third of the systolic pressure plus two-thirds of the diastolic pressure. At noon they consumed a light lunch. From 13.00 until 14.00 h the individuals were given a water load of 25 ml/kg. During the following hours the water load was maintained by drinking a volume of water equal to their 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 mosm/kg, three consecutive urine portions were sampled. Blood was taken in the middle of each 20 min period. Plasma and urine were analysed for osmolality, sodium, potassium and creatinine according to standard hospital procedures. PRA was determined radio-immunologically according to a modification of the method described by Haber *et al.* (1969) (incubation of undiluted plasma for 1 h at 37°C and pH 5.6, followed by deproteinization of the plasma with 4 N ammonia:acetone 1:9). PA was assessed by a non-chromatographic direct radio-immunoassay according to Ogihara *et al.* (1977).

Clearances were calculated according to standard formulae. The following parameters were calculated for an estimation of proximal and distal sodium reabsorption per GFR:

$$fC_{H_2O} = \text{fractional maximal free-water clearance}$$

$$= \frac{(U_v \max - C_{osm})}{GFR} \cdot 100\% \ (\%)$$

$$fPR_{Na} = \text{fractional proximal resorption of sodium}$$

$$= 100 - \frac{(U_{Na+K} \cdot U_v \max)}{F_{Na}} \cdot 100\% + fC_{H_2O} \ (\%)$$

fDR_{Na} = fractional distal sodium absorption

$$= \frac{(U_v max - C_{osm})}{\frac{(U_{Na+K} \cdot U_v max)}{P_{Na}}} \cdot 100\,(\%)$$

Where:

C_{osm} = osmolar clearance (ml/min)
U_{Na+K} = sum of urinary concentrations of sodium and potassium (μmol/l)
F_{Na} = filtered sodium (μmol/l)
P_{Na} = plasma concentration of sodium (μmol/l)
$U_v max$ = maximal diuresis during free water clearance (ml/min)

Statistical evaluation

Values are expressed as means ± s.e. mean. Differences between placebo and the first and last day of nicardipine therapy were evaluated by the paired Wilcoxon test. Difference in age between groups were computed with the unpaired Wilcoxon test. Differences in responses between groups were calculated by two-way analysis of variance with unequal proportional subclass sizes.

Results

The hypertensive patients were significantly older than the healthy volunteers ($P < 0.005$).

Haemodynamic parameters

Table 2 shows the effects of nicardipine on the parameters measured.

Both the normotensive and the hypertensive group showed a decrease in blood pressure. This decrease was of the same order for both groups, that is, 4% after the first dose and 6% after one week compared with placebo. Both groups showed a fall in MAP that was significant ($P < 0.05$), but not significantly different in the hypertensive and the normotensive groups.

Body weight decreased slightly in both groups, but reached significance only in the hypertensive group after 1 week of treatment ($P < 0.01$). The difference between the groups in fall in body weight, however, was not significant.

Log PRA increased slightly in both groups. A significant change in log PRA was shown in the hypertensive group after the first dose ($P < 0.05$). Log PA decreased slightly in the normotensive group with significance after the first dose ($P < 0.01$), but remained unchanged in the hypertensive group.

Table 2 Effects of nicardipine

	Last day placebo		*First day nicardipine*		*Last day nicardipine*	
	NT	*HT*	*NT*	*HT*	*NT*	*HT*
Body weight (kg)	74.4 ± 2.0	82.0 ± 3.2			74.2 ± 1.8	8.10 ± 3.6*
Systolic BP (mm Hg)	120 ± 4	139 ± 3	113 ± 4**	134 ± 4	113 ± 4	133 ± 5
Diastolic BP (mm Hg)	70 ± 3	102 ± 3	66 ± 3	96 ± 3*	66 ± 2	95 ± 4*
MAP (mm Hg)	83 ± 4	115 ± 3	80 ± 3*	109 ± 3*	78 ± 4*	108 ± 4*
Heart rate (beats/min)	57 ± 4	62 ± 7	57 ± 3	69 ± 4	57 ± 3	71 ± 5
Log PRA (fmol $l^{-1} s^{-1}$)	2.57 ± 0.07	2.64 ± 0.09	2.62 ± 0.05	2.81 ± 0.07*	2.66 ± 0.06	2.69 ± 0.09
Log PA (pmol/l)	2.48 ± 0.05	2.25 ± 0.07	2.37 ± 0.05*	2.39 ± 0.07	2.33 ± 0.06	2.30 ± 0.06
$U_v max$ (ml/min)	18.1 ± 1.3	14.8 ± 1.5	23.4 ± 1.6*	17.7 ± 1.4	24.6 ± 1.2**	18.6 ± 2.6*
U_{Na} (mmol/min)	177 ± 8	101 ± 5	429 ± 21*	161 ± 8*	480 ± 24**	332 ± 16**
fC_{Na} (%)	1.0 ± 0.1	0.6 ± 0.1	2.1 ± 0.1*	0.9 ± 0.1	2.6 ± 0.0**	1.3 ± 0.1
fC_{H_2O} (%)	11.0 ± 0.9	10.3 ± 1.7	12.5 ± 0.7*	11.0 ± 1.4	13.9 ± 0.8*	9.3 ± 1.5

All values obtained 1–3 h after oral medication of placebo or 20 mg nicardipine both three times daily during the week.
NT = normotensive, HT = hypertensive
U_{Na} = Urinary excretion of sodium
fC_{Na} = fractional clearance of sodium
fC_{H_2O} = fractional clearance of free water
* $P < 0.05$ compared to placebo values
** $P < 0.01$ compared to placebo values

Renal function during water loading

Maximal diuresis was significantly increased in both groups ($P < 0.01$) after 1 week nicardipine treatment. Creatinine clearance measured during water loading in the normotensive group remained unchanged throughout nicardipine treatment in comparison with the placebo period. After 1 week treatment the creatinine clearance of the hypertensive group had increased significantly ($P < 0.01$, Figure 1). However, differences in increase of GFR between the groups were not significant ($P = 0.13$). Both groups showed an increase of fractional sodium clearance which was significant in the normotensive group ($P < 0.01$) after 1 week.

The proximal reabsorption of sodium (fPR_{Na}) fell significantly in the normotensive group ($P < 0.01$), but remained unchanged in the hypertensive group (Figure 2). However, differences between the groups were not significant ($P = 0.11$) after 1 week. The fractional clearance of free water fell significantly in the normotensive group.

The distal reabsorption of sodium (fDR_{Na}) fell significantly in the normotensive group after the first dose ($P < 0.05$), and in both groups after one week ($P < 0.05$) (Figure 3). The differences in fall in fDR_{Na} between the groups was significant only after the first dose ($P < 0.05$).

Side-effects occurred mainly in the hypertensive group. One hypertensive patient withdrew on the third day of nicardipine treatment due to severe flushing and headaches. The most common complaints were headaches and tiredness, but the effects were mostly transient and mild, and often present during the placebo week.

Discussion

In 1972, Murakami *et al.* described an antihypertensive effect of nifedipine during treatment of patients with angina pectoris. They studied this effect in patients with essential hypertension, in whom the blood pressure was lowered by a decrease in peripheral resistance, with a concomitant increase of cardiac output and heart rate (Murakami *et al.*, 1972). The antihypertensive effect of nifedipine had been reported to correlate positively with the initial pressure (Heidland, 1982; McGregor, 1982) and was not observed in normotensive subjects (Leonetti *et al.*, 1982).

The antihypertensive effect of nicardipine has been documented previously (Takabatake *et al.*, 1982; Jones *et al.*, 1983).

This study shows a reduction of blood pressure in both healthy volunteers and hypertensive patients of about 4% following an initial dose of nicardipine with further reduction to about 6% after a week. Because of the open design of the study, however, it should be noted that the fall in blood pressure could be due to other effects, e.g. acclimatisation, rather than to a true drug effect. This minor fall in blood pressure is clinically unimportant.

The normotensive patients were younger than the hypertensives, and the differences discussed below may be related to age rather than to hypertension. The hypertensive group showed an increase in heart rate, an effect shown previously and found to be dose-dependent (Taylor *et al.*, 1982). Although the decrease in blood pressure was similar in both groups there was no change in the heart rate of the normotensives.

PRA was slightly increased in hypertensive patients in this study, and there was a slight decrease in PA following nicardipine administration. These data are in accordance with previous results for nifedipine. An increase in PRA has been reported in some studies (Aoki *et al.*, 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 unchanged

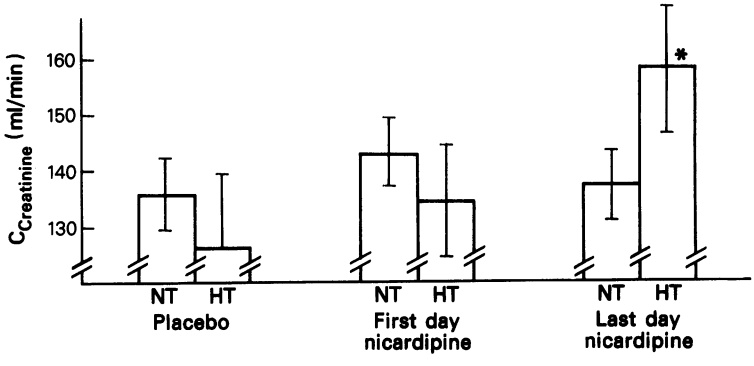

Figure 1 Creatinine clearance. NT normotensive; HT hypertensive; *$P < 0.05$.

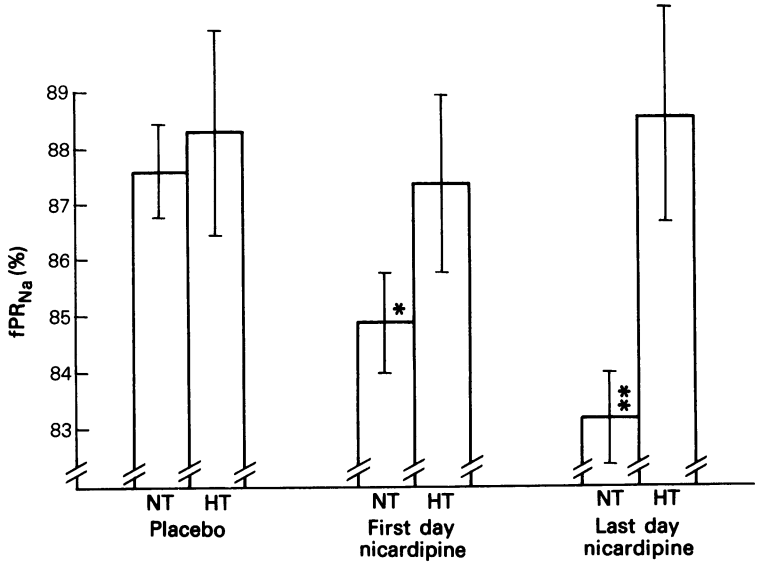

Figure 2 Proximal reabsorption of sodium. NT normotensive; HT hypertensive; $*P < 0.05$, $**P < 0.01$.

(Hiramatsu, 1982) or even decreased (Heidland, 1982; Thibonnier *et al.*, 1980) despite an increase in PRA. This could be explained by a decrease of the sensitivity of the zona glomerulosa to angiotensin II (Millar, 1982). It is evident that PRA stimulation, if present at all, is seen much less than with other vasodilators.

Patients treated with vasodilators which act on resistance vessels often develop sodium retention. However, after an intravenous dose of nifedipine GFR and renal blood flow increased markedly, as did diuresis and urinary excretion of sodium (Klütsch, 1972; Yokoyama & Kaburagi, 1983). McCrorey *et al.* (1979) found a tubular natriuretic effect independent of GFR and renal blood flow.

Previous work with nicardipine has illustrated strong diuretic effects (Yokoyama & Kaburagi, 1981). During intravenous infusion of nicardipine (33 μg/min) patients with essential hypertension had increases in urinary volume of 115%; in urinary sodium excretion of 95%; and in GFR of 62%. These authors also found that patients with glomerulonephritis had absent

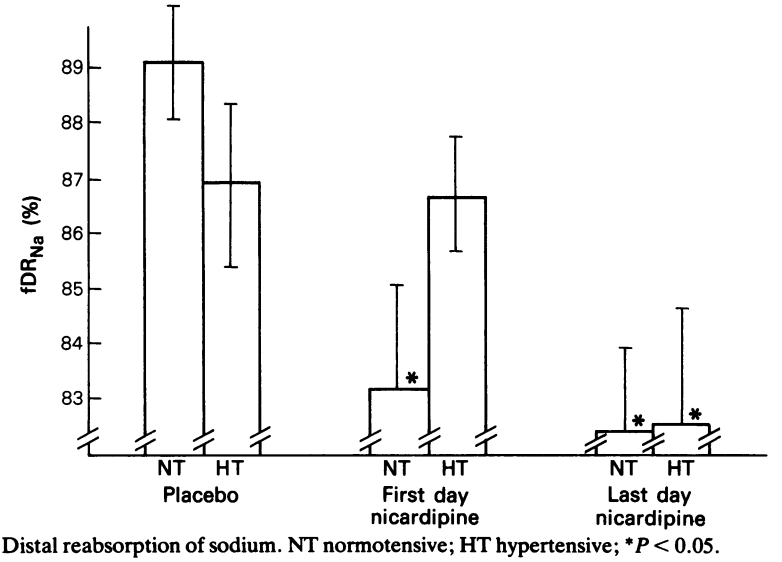

Figure 3 Distal reabsorption of sodium. NT normotensive; HT hypertensive; $*P < 0.05$.

(GFR) or less pronounced (sodium excretion and urinary volume) responses. The authors suggested a difference in renal pathophysiology between the two groups, and particularly an increased calcium-dependent vascular tone in essential hypertension.

After 1 week of treatment with nicardipine our results show that there is still a natriuretic effect, during waterloading and measured 2 h after administration of the drug. There was only a 0.2 kg decrease in body weight in the normotensive group, and a 1 kg decrease in the hypertensive group. Therefore, we assume that the natriuretic effect of nicardipine is short-acting and partially compensated during 24 h with this dose and frequency of administration.

After the first oral dose we found GFR increased by 6% in hypertensives and by 5% in the normotensives. After 1 week GFR had increased in the hypertensive group by 25% in contrast to 1% in the normotensive group. Although the increase in GFR in the hypertensive group was more pronounced after 1 week of treatment than in the normotensive group, this increase was still lower than the 62% noted during intravenous administraion (Yokoyama & Kaburagi, 1981). However, the increases in sodium excretion in our study were comparable to those found with intravenous nicardipine in essential hypertensives. Our results indicate that the excretion of sodium is not caused only by an increase of GFR, but also by a decrease in tubular absorption in the proximal (in the normotensive group) and distal segments of the nephron.

In the normotensive group the natriuretic effect was caused by decreased tubular reabsorption of sodium. In the hypertensive group however, the natriuresis was achieved mainly by an increase of GFR and also by a slight distal effect. The possibility that nicardipine interferes with measurements of creatinine has not been excluded, but this would not explain differences between the two groups. The higher maximal diuresis and lower calculated proximal sodium reabsorption in the normotensives could probably be ascribed to their higher salt intake when compared to the hypertensives. The fact that in the hypertensive group fPR_{Na} hardly changed could indicate an abnormality in the hypertensive kidney.

In conclusion, the results of our study suggest that there may be differences in the effects of nicardipine on renal function between essential hypertensives and normotensives, although most of these differences did not reach statistical significance. This would be consistent with the hypothesis that abnormalities in the movement of calcium ion through the cell membrane are present in the hypertensive kidney (Aoki *et al.*, 1978). The results also show that nicardipine has a moderate and short-acting natriuretic action.

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