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Calcium channel blockers — are they diuretics?

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1 Seven untreated patients with essential hypertension but without target organ damage were admitted to hospital. Urine was collected the following day from 08.00 to 13.00 h, 13.00 to 18.00 h, and 18.00 to 08.00 h. The protocol was repeated the next day following 30 mg oral nicardipine. Intra-arterial blood pressure (IABP), plasma volume, and plasma renin activity (PRA) also were measured daily.

2 Following the single-dose study, the patients were treated as outpatients and received oral nicardipine 20, 30, or 40 mg four times daily. They were readmitted 2 months later for further study, at which time the protocol was repeated.

3 Urine output between 08.00 and 13.00 h significantly increased after the single- and multiple-dose studies. Following the single-dose study, this diuresis was associated with a natriuresis. Urine output increased over the 24 h following multiple-dose treatment, but this increase was not statistically significant.

4 During the multiple-dose 24 h study, there was an increase in urinary potassium ($P < 0.05$).

5 Mean IABP was reduced significantly after the single-and multiple-dose studies ($P < 0.02$ and < 0.05, respectively).

6 During the study, there were no significant changes in plasma volume, weight, or plasma renin activity.

Keywords calcium channel blockers diuretics nicardipine

Introduction

Calcium channel blockers are now accepted therapy in the treatment of essential hypertension, and their efficacy as monotherapy is well established (Jones *et al.*, 1983; McLeay *et al.*, 1983). A possible advantage of these drugs over vasodilators such as hydrallazine is that after chronic treatment the baroreceptor resets, and heart rate returns to normal (McLeay *et al.*, 1983). A further suggested advantage of calcium channel blockers over vasodilators such as minoxidil is the ability of the former drugs to increase sodium and water loss via the kidney, at least in the short term (Klütsch *et al.*, 1972; Leonetti *et al.*, 1982; van Schalk *et al.*, 1984). The aim of this study was to observe the effects on intra-arterial blood pressure, urinary volume, and urinary electrolytes of single and multiple doses of nicardipine, a calcium channel blocker similar to nifedipine. The drug has a half-life of approximately 6–8 h.

Methods

We studied seven patients with essential hypertension who had no evidence of target organ damage. Essential hypertension was defined as three separate outpatient cuff pressure readings of 140/90 mm Hg or more, phase V indicating diastolic pressure. Evidence of target organ damage was defined as a history of ischaemic heart disease or cerebrovascular disease, presence of peripheral vascular disease, left ventricular

hypertrophy, and renal impairment. Secondary hypertension was excluded by clinical examination, estimation of serum electrolytes and urinary catecholamines, and intravenous pyelography where appropriate. All patients had been untreated for at least 2 months before the study; there were four males and three females, average age 49 years (range 36–64 years). The average outpatient blood pressure of the group was 183/111 ± 28/12 mm Hg.

All patients gave informed consent, and the study was fully approved by the Hospital Ethics Committee. Patients were studied in hospital, and urine was collected between 08.00 and 13.00 h, 13.00 and 18.00 h, and 18.00 and 08.00 h. Each patient drank 350 ml of fluid during the 08.00–13.00 h period, but intake was unrestricted thereafter. Subjects were instructed to add dietary salt as they would at home. On the following day, patients were given 30 mg of nicardipine orally at 08.00 h and the protocol was then repeated, the final urine collection finishing at 18.00 h. For the next 2 months, patients were treated with nicardipine 20, 30 or 40 mg three times daily (08.00, 14.00, 20.00 h), depending on blood pressure response. Following this outpatient period the patients were readmitted for further study, and the protocol was repeated as above over 24 h.

On each occasion intra-arterial blood pressure (IABP) was measured from the brachial artery in the nondominant arm via a 1 mm diameter Grand Jean cannula connected to a Grass Polygraph physiological recorder through a miniature transducer. Cannulation occurred at 09.00 h on the first day and IABP was measured with the patient supine between 10.00 and 11.00 h on the first and second days; the same procedure was repeated after the multiple-dose study. Plasma volume was measured following 1 h of supine rest during the first day and after the multiple-dose study using ^{125}I-labelled human albumin. Plasma renin activity (PRA) was measured on all three occasions following 1 h of supine rest using Waite's radioimmunoassay (Waite, 1973). Indirect cuff pressure was measured on admission, during control and multiple-dose studies using a Hawksley Random Zero sphygmomanometer.

Results were analysed using Student's paired *t*-test for normally distributed data, Wilcoxon's signed rank test being used for nonparametric data. The level of statistical significance was taken as $P < 0.05$, and results are shown as mean values ± s.d.

Results

There was a significant increase in urine output between 08.00 and 13.00 h following the single dose (401 ± 209 *vs* 664 ± 364 ml, $P = 0.05$) and multiple doses (401 ± 209 *vs* 629 ± 180 ml, $P = 0.05$) of nicardipine (Figures 1 and 2). The diuresis following the single dose was associated with a natriuresis (urinary Na^+ 27 ± 16 *vs* 58 ± 38 mmol, $P \leqslant 0.05$). After the multiple doses the diuresis was not associated with natriuresis (urinary Na^+ 27 ± 16 *vs* 35 ± 21 mmol, $P \geqslant 0.05$). In Figure 1 the measured fall in urinary volume, urinary sodium and potassium occurred in the same patient. Urine output throughout the 24 h following the multiple dose period increased, but the difference did not reach statistical significance (1772 ± 441 control *vs* 2014 ± 251 ml). Potassium excretion was significantly increased (Figure 3) during the multiple dose study (urinary K^+ 43 ± 22 control *vs* 50 ± 25 mmol, $P < 0.05$). Serum potassium remained unchanged (3.9 ± 0.4 control *vs* 3.8 ± 0.3 mmol).

Mean IABP fell from 132 ± 14 to 117 ± 12 mm Hg after the single dose ($P < 0.02$) and to 110 ± 20 mm Hg after the multiple dose treatment ($P < 0.05$). Indirect measurement

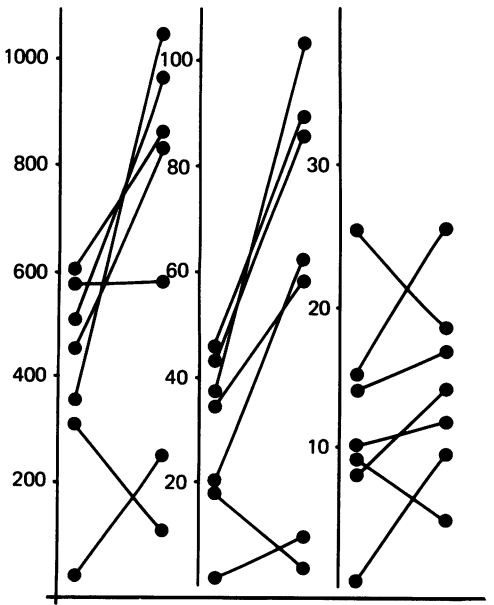

Figure 1 Urine volume and electrolytes, control *vs* single dose, 08.00–13.00 h.

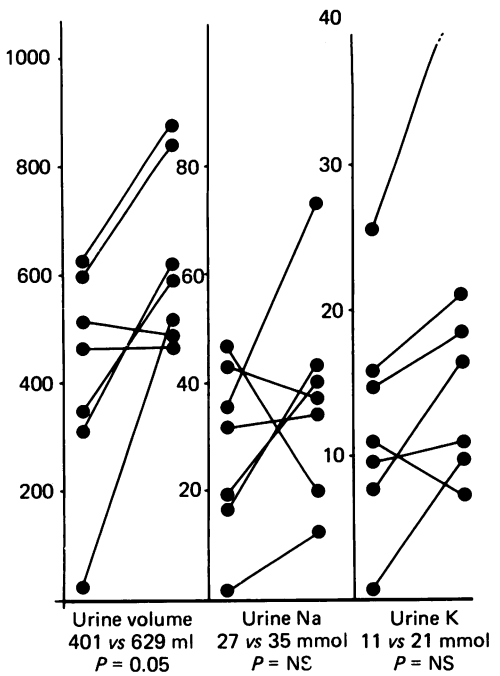

Figure 2 Urine volume and electrolytes, control *vs* multiple dose, 08.00–13.00 h.

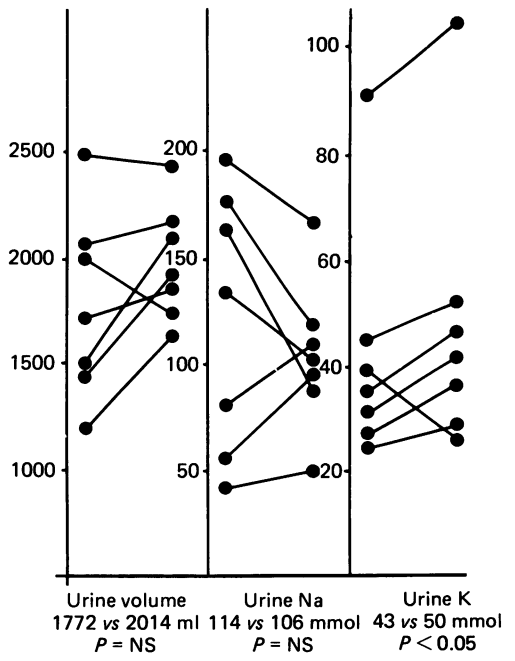

Figure 3 Urine volume and electrolytes, control *vs* multiple dose, 24 h period.

showed that blood pressure fell from 174/104±28/20 to 150/97±18/14 mm Hg after multiple doses, $P < 0.02$ for systolic and $P < 0.05$ for diastolic pressure. There was no relationship between percentage fall in IABP and percentage increase in urine output ($n = 7$, $r = 0.51$, $P =$ NS single dose; $n = 7$, $r = 0.60$, $P =$ NS multiple dose).

Neither plasma volume (39±5 control *vs* 37±6 ml/kg) nor weight (71±10 control *vs* 70±9 kg) changed significantly following multiple-dose treatment. Plasma renin activity was unchanged after the single dose (1.0±0.6 control *vs* 0.9±0.7 nmol l^{-1} h^{-1}, $P =$ NS) and the multiple doses (1.0±0.6 *vs* 1.2±0.6 nmol l^{-1} h^{-1}, $P =$ NS).

Discussion

We observed significant increases in urine output following both the single-dose and multiple-dose treatment, but only during the 08.00 to 13.00 h period; urine output during the 24 h period was increased during the multiple-dose study, but not significantly so. These findings, combined with the observation of a natriuresis following the single-dose and a kaliuresis following multiple-doses in a 24 h period, strongly suggest an effect on renal tubular function. Exactly how these effects were brought about cannot be ascertained from the information in this study.

Some recent work in dogs (Dietz *et al.*, 1983) showed that both nifedipine and verapamil, in doses which did not reduce blood pressure, produced marked increases in urinary flow and urinary sodium; these changes seemed to occur irrespective of alterations in renal blood flow and despite consistently unchanged values of creatinine clearance and filtration fraction. Other workers (Dibona & Sawin, 1984) have had similar results using felodipine in rats, although van Schalk *et al.* (1984) found an increased glomerular filtration rate to be mainly responsible for the natriuretic effect of nicardipine in ten patients with essential hypertension.

We observed no consistent effect on PRA following a single dose of nicardipine, although this may have been because the PRA was measured 7 h following administration of nicardipine, when the hypotensive effects of the drug would have been diminishing. Our failure to observe any change in PRA measured following the multiple doses is consistent with our previous findings using nifedipine (McLeay *et al.*, 1983).

In conclusion, this study suggests that nicardipine in some way alters renal tubular function in patients with essential hypertension and that this effect persists following multiple-dose treatment. Further metabolic-balance studies are necessary to evaluate the long-term effects of nicardipine on renal function.

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