Diuretic and natriuretic effects of nifedipine in healthy persons

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- 1 We have studied the diuretic and natriuretic effects and the tubular site of action of nifedipine using free water clearance (CH_2O) and lithium clearance.
- 2 We have compared the effects of nifedipine (10 mg p.o.) with those of placebo and of frusemide (40 mg p.o.) in seven healthy volunteers during maximal water diuresis.
- 3 Compared with placebo, nifedipine caused a significant rise in urinary flow rate and CH_2O , paralleled by significant increases in fractional excretion of sodium and lithium. The rise in sodium excretion was not accompanied by an increase in potassium excretion.
- 4 Frusemide caused increases in sodium and lithium excretion, comparable with the effects seen after nifedipine. CH_2O did not change however.
- 5 Our study demonstrates that nifedipine has a clear diuretic and natriuretic effect in healthy volunteers, which is predominantly established by interference with proximal tubular sodium reabsorption. Lithium clearance did not allow us to differentiate between nifedipine and frusemide effects, thus questioning the reliability of lithium as a marker of proximal tubular sodium reabsorption.

Keywords nifedipine natriuresis frusemide free water clearance lithium clearance

Introduction

Calcium antagonists are potent antihypertensive drugs, which act through peripheral vasodilatation. They differ from traditional vasodilators by increasing renal water and sodium excretion (Zanchetti & Leonetti, 1985), a feature noted by Klütsch *et al.* (1972) who treated hypertensive patients with nifedipine. More recently this diuretic and natriuretic capacity has been confirmed for a number of related calcium antagonists e.g. nifedipine (Ene *et al.*, 1985), nitrendipine (Ene *et al.*, 1985; Wallia *et al.*, 1985), nicardipine (van Schaik *et al.*, 1984), and felodipine (Sluiter *et al.*, 1985). As reviewed elsewhere, several mechanisms could account for this natriuretic effect, and the tubular site of action is still debated (Zanchetti & Leonetti, 1985). In rat studies using micropuncture techniques interference of calcium antagonists with sodium re-

absorption in the distal tubule has been demonstrated (DiBona & Sawin, 1984). In human studies data on the site of action of diuretic agents have to be obtained with indirect clearance techniques, mostly involving measurements of the fractional excretion of sodium and free water during maximal water diuresis (Seldin & Rector, 1972; Puschett, 1981). Data obtained with these techniques should be interpreted with caution however, since there are several pitfalls when using this method (reviewed by Seldin & Rector, 1972). Recently the use of lithium as a suitable marker of proximal tubular sodium transport has been proposed (Thomsen, 1984). We have studied the diuretic and natriuretic site of action of nifedipine in healthy volunteers using free water clearance as well as lithium clearance. Furthermore we have compared the effects of

nifedipine with those of frusemide, a potent diuretic drug with a known site of action. Our results demonstrate that the natriuretic effect of nifedipine is mainly established by interference with proximal tubular sodium reabsorption. The reliability of lithium as a marker of sodium transport in the proximal convoluted tubule is debatable.

Methods

We studied seven healthy volunteers (four men and three women) with a mean age ($\pm$ s.d.) of 24 ± 3 years, a mean body weight of 71 ± 7 kg, and a mean endogenous creatinine clearance (ECC) of 136 ± 19 ml min⁻¹. All experiments were done at the same time of the day (from 09.00 h till 13.00 h) to exclude influences of diurnal rhythms. The evening before the experiment each volunteer took 600 mg of lithium carbonate (16.2 mmol lithium). After consuming a light breakfast (coffee and tea were not allowed) the volunteers came to the ward at 09.00 h. A water diuresis was induced by an oral water load of 25 ml kg⁻¹ body weight given from 09.00 h to 10.00 h. Urinary losses were replaced by an equivalent intake of tap water thereafter. Urine was collected by spontaneous voiding. Except for standing to void the volunteers were supine during the investigation. Each volunteer was studied on three occasions within a period of 4 weeks. Placebo, frusemide (Lasix® 40 mg), or nifedipine (Adalat® 10 mg) were given orally in a single blinded, randomized way at 11.00 h. Until 13.00 h urine samples were collected every 30 min for determination of volume, creatinine, sodium, potassium, lithium, and osmolality. Blood samples were drawn at the beginning and the end of each urine collection period for determination of creatinine, osmolality, sodium, potassium, lithium, and haemoglobin. Blood pressures and heart rates were measured every 5 min with an automatic device (Arteriosonde 1225). Blood pressure values used for calculations are the means of four consecutive readings in each clearance period. Lithium concentrations in urine and blood were measured by atomic absorption spectrophotometry. All other variables were measured with standard techniques. Clearances as well as proximal and distal sodium reabsorption were calculated according to standard formula (Seldin & Rector, 1972; see appendix). ECC was used as a marker of glomerular filtration rate (GFR). Free water clearance (CH₂O) was calculated as urinary flow rate (V) minus osmolal clearance (Cosm). The fractional excretion (Fe) of a substance was defined as the

renal clearance of that substance divided by ECC, and expressed as a percentage. Fractional distal sodium reabsorption was calculated corrected for total tubular load ($ECC \times P_{Na}$) and corrected for distal tubular load ($V \times P_{Na}$). Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one third of the pulse pressure.

Differences from placebo were evaluated using Student's *t*-test for paired observations if a normal distribution applied, or with Wilcoxon rank-sum test. A *P* value of less than 0.05 was considered significant. Unless otherwise stated all values are expressed as means $\pm$ s. e. mean.

All volunteers gave written informed consent. The study protocol was approved by the Hospital Ethics Committee.

Results

Haemodynamic effects

Compared with placebo, MAP was significantly lower only from 30 to 90 min after nifedipine administration, due to a lower diastolic blood pressure (placebo 83.3 ± 4.3 and 82.2 ± 3.4 mmHg, nifedipine 71.1 ± 2.5 and 71.0 ± 3.3 mmHg; $P < 0.01$), whereas systolic blood pressure was unchanged. This decrease in diastolic blood pressure on nifedipine was accompanied by a significant rise in heart rate 60–90 min after administration of the drug (placebo 54.1 ± 3.1 beats min⁻¹, nifedipine 62.5 ± 1.8 beats min⁻¹; $P < 0.05$). No significant changes as compared with placebo were observed after frusemide administration. Four volunteers had complaints of flushing or a slight headache after nifedipine administration.

Diuretic and natriuretic effects

At the beginning of the experimental periods in all volunteers a water diuresis was established, urinary flow rate ranging from 11.2 to 20.8 ml min⁻¹ and in all cases urinary osmolality was below 80 mosmol kg⁻¹. Serum lithium concentration ranged from 0.15 to 0.29 mmol l⁻¹ at the beginning of the experimental periods, a value well below the toxic and therapeutic level. ECC showed a slight and short-lasting increase after nifedipine, reaching its maximum in the third clearance period (60–90 min) after nifedipine administration (Table 1). Frusemide did not influence ECC.

Nifedipine caused a consistent rise of urinary flow rate (Figure 1) reaching a maximum mean value of 22.5 ± 2.0 ml min⁻¹ in the third clearance

Table 1 Effects of nifedipine and frusemide on creatinine, osmolal, and potassium clearance, and on sodium reabsorption

	Period 1 0–30 min	Period 2 30–60 min	Period 3 60–90 min	Period 4 90–120 min
<i>ECC (ml min⁻¹)</i>				
p	136 ± 7	138 ± 9	136 ± 10	134 ± 8
f	132 ± 9	134 ± 10	131 ± 8	133 ± 10
n	139 ± 11	143 ± 12	153 ± 12**	142 ± 11
<i>Cosm (ml min⁻¹)</i>				
p	3.21 ± 0.25	3.17 ± 0.25	3.24 ± 0.37	3.22 ± 0.47
f	3.51 ± 0.57	6.71 ± 1.80	6.72 ± 1.59	5.65 ± 0.55**
h	3.70 ± 0.29	5.08 ± 0.47***	5.64 ± 0.64**	5.01 ± 0.68*
<i>C_K (ml min⁻¹)</i>				
p	9.4 ± 2.5	8.6 ± 2.2	6.4 ± 1.4	5.6 ± 1.3
f	13.9 ± 2.8	21.4 ± 5.0	20.9 ± 5.3*	19.3 ± 3.9*
n	12.8 ± 3.0	8.8 ± 3.0	8.2 ± 2.8	6.8 ± 3.4
<i>fPRNa⁺ (%)</i>				
p	89.9 ± 1.0	90.9 ± 0.9	89.9 ± 0.9	90.3 ± 1.1
f	89.1 ± 0.7	87.2 ± 0.9	87.3 ± 1.0	88.2 ± 0.7*
n	89.0 ± 1.0	86.1 ± 1.0**	86.1 ± 1.0**	86.2 ± 1.3*
<i>fDRNa⁺ (%)</i> <i>(ECCxNa⁺)</i>				
p	9.1 ± 1.0	9.0 ± 0.9	9.0 ± 0.9	8.8 ± 1.0
f	9.8 ± 0.7	9.7 ± 0.7	9.4 ± 0.6	9.1 ± 0.6
n	9.7 ± 1.0	11.5 ± 1.0*	11.4 ± 0.9**	11.4 ± 1.1*
<i>fDRNa⁺ (%)</i> <i>(VxNa⁺)</i>				
p	80.1 ± 1.7	80.2 ± 1.7	79.7 ± 1.9	79.1 ± 2.4
f	81.2 ± 2.7	70.7 ± 5.3	69.2 ± 4.4	70.6 ± 1.8*
n	79.7 ± 1.7	77.1 ± 1.6*	76.4 ± 1.8*	77.2 ± 2.1

p = placebo; f = frusemide; n = nifedipine. Drugs were administered at $t = 0$ min. Significant differences as compared with placebo are marked with an asterisk; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

period, compared with 15.2 ± 1.2 ml min⁻¹ in the same period on placebo ($P < 0.01$). This increase in urinary flow rate was paralleled by significant increases of FeNa (placebo $1.0 \pm 0.2\%$, nifedipine $2.5 \pm 0.3\%$; $P < 0.01$), FeLi (placebo $21.8 \pm 1.4\%$, nifedipine $28.2 \pm 2.2\%$; $P < 0.01$), and Cosm (placebo 3.24 ± 0.37 ml min⁻¹, nifedipine 5.64 ± 0.64 ml min⁻¹; $P < 0.01$) (Figure 2, Table 1). Urinary flow rate rose more than proportional to the rise in Cosm as evidenced by the increase in CH₂O (Figure 1). CH₂O corrected for ECC was also higher on nifedipine (placebo $8.85 \pm 0.93\%$, nifedipine $11.17 \pm 0.91\%$; $P < 0.01$). The rise in sodium excretion on nifedipine was not accompanied by an increase in potassium excretion (Table 1). Calculation of fractional proximal sodium reabsorption demonstrated a significant decrease in proximal tubular sodium reabsorption of approximately 3–4% after nifedipine (Table 1). Although distal tubular reabsorption corrected

for total tubular load increased, this increase was not large enough to match for the increased distal tubular load, as is evidenced by the decreased fractional distal tubular sodium reabsorption when corrected for distal tubular load (Table 1).

The effects of frusemide on renal excretory function are also shown in Table 1 and Figures 1 and 2. Individual responses to frusemide varied considerably. In some a diuretic and natriuretic effect was not noted before the fourth clearance period. Although some volunteers demonstrated an enormous increase of urine flow, mean urinary flow rate did not change significantly. Frusemide caused significant increases of Cosm, FeNa and FeLi, comparable to nifedipine (Table 1, Figure 2). CH₂O, however, did not change on frusemide (Figure 1). The increased sodium excretion after frusemide administration was accompanied by an increased secretion of potassium as evidenced by the increased values of potassium clearance

Figure 1 Urinary flow rate and free water clearance (CH₂O) after administration of placebo (●), nifedipine (■), or frusemide (▲) at $t = 0$ min. Significant differences from placebo are marked. * $P < 0.05$; ** $P < 0.01$.

Figure 2 Fractional excretion of Na and Li after administration of placebo (●), nifedipine (■), or frusemide (▲) at $t = 0$ min. Significant differences from placebo are marked. * $P < 0.05$; ** $P < 0.01$.

Table 2 Maximal changes after nifedipine and frusemide administration as compared with placebo

	Nifedipine	Frusemide
FeNa (%)	1.6 ± 0.3*	3.0 ± 1.0**†
FeLi (%)	6.8 ± 1.6*	7.2 ± 1.5*
CH ₂ O (ml min ⁻¹)	4.5 ± 0.9*	0.4 ± 0.7†
Urine flow (ml min ⁻¹)	7.4 ± 1.2*	3.9 ± 1.9

Values are given as means ± s.e. mean *; Significantly different from placebo ($P < 0.05$). †; Significantly different from nifedipine ($P < 0.05$).

(C_K) (Table 1). Fractional proximal sodium reabsorption and fractional distal sodium reabsorption corrected for distal sodium load were both decreased by frusemide (Table 1).

We additionally have analysed the mean maximal effects of nifedipine and frusemide using values of the period of the maximal natriuretic

effect of the drug for each volunteer, as compared with values in the same period on placebo. Results are given in Table 2.

Discussion

We have studied the effects of nifedipine on renal excretory function in healthy volunteers, examined under conditions of maximal water diuresis. We have observed an evident increase of urinary flow rate and urinary sodium excretion, whereas urinary potassium excretion remained unchanged. These findings confirm our earlier observations with the related drug felodipine (Sluiter *et al.*, 1985), and agree with those of others who recently have demonstrated the diuretic and natriuretic properties of nitrendipine (Ene *et al.*, 1985; Wallia *et al.*, 1985) and nifedipine (van Schaik *et al.*, 1984). It is clear from our study that diuresis and natriuresis occur

despite the blood pressure lowering effect of the drug. In this respect calcium antagonists differ from traditional antihypertensive vasodilators, which almost invariably cause salt and water retention.

Since a study of the possible mechanisms of the diuretic and natriuretic properties of nifedipine was beyond the scope of the current investigation, we did not perform extensive renal haemodynamic studies and have only used creatinine clearance as a marker of GFR. Nifedipine caused a transient increase in ECC, which is in agreement with our earlier studies on felodipine, which appeared to cause transient increases of ECC as well as of inulin clearance. Frusemide did not influence creatinine clearance, which is in agreement with studies of others who did not find any influence of frusemide on GFR using inulin clearance (Puschett & Goldberg, 1968). Therefore, it seems unlikely that the use of creatinine clearance instead of inulin clearance could have substantially influenced our results.

We have used free water clearance as well as lithium clearance to elucidate the possible site of action of nifedipine. Free water clearance increased after nifedipine administration. A similar observation has been made by Wallia *et al.* (1985) and van Schaik *et al.* (1984) who studied the effects of nitrendipine, and nicardipine respectively during maximal water diuresis. An increase of free water clearance is generally viewed as evidence for interference with sodium reabsorption at a site proximal to the thick ascending limb of Henle's loop, e.g. the proximal tubule or the inner medullary segment of Henle's loop (Seldin & Rector, 1972; Puschett, 1981). It is difficult, however, to draw firm conclusions, since this method has several pitfalls. The underlying assumption that the entire nephron distal from Henle's loop is completely water-impermeable during maximal water diuresis has been invalidated by results of animal studies (Morgan & Berliner, 1968; Jamison *et al.*, 1971). Theoretically, interference of a drug with water reabsorption in the collecting tubule could also explain the increased free water clearance, that we found.

To obviate this problem we have used lithium clearance in addition to free water clearance. As reviewed elsewhere, lithium could be a useful marker of proximal tubular sodium reabsorption (Thomsen, 1984). Micropuncture studies in the rat have demonstrated that no lithium is reabsorbed beyond an early distal tubular puncture site (Hayslett & Kashgarian, 1979). The increase in lithium excretion after administration of nifedipine is thus suggestive for interference of the drug with proximal tubular sodium reabsorption.

Taken together, both clearance methods indicate that the diuretic and natriuretic effect of nifedipine is established by inhibition of proximal tubular sodium reabsorption. However, the resultant increase in distal tubular flow rate and distal tubular sodium load did not cause an increased potassium excretion, as would have been expected (Good & Weight, 1979; Khuri *et al.*, 1975). This points to an additional interference of nifedipine with distal tubular function, specifically at the $\text{Na}^+ - \text{K}^+$ exchange site. Blockade of the $\text{Na}^+ - \text{K}^+$ exchange could explain the decrease in fractional distal sodium reabsorption (relative to distal tubular load).

In most animal studies the increase in sodium excretion after administration of calcium antagonists is accompanied by an increase in potassium excretion (DiBona & Sawin, 1984; Yamaguchi *et al.*, 1974; Abe *et al.*, 1982; Brown & Churchill, 1983). These findings are compatible with a predominant proximal effect of these drugs, and suggest an absence of interference with $\text{Na}^+ - \text{K}^+$ exchange. Interpretation is complicated by the apparently contradictory finding that in rats and dogs, using micropuncture techniques and stop flow procedures respectively, predominant interference of calcium antagonists with distal tubular sodium reabsorption has been demonstrated (DiBona & Sawin, 1984; Yamaguchi *et al.*, 1974; Nagao *et al.*, 1985). We cannot explain these inconsistencies in the animal studies, but the effects of calcium antagonists may vary, depending on the experimental conditions, the type and dosage of the drug used, and the animal species studied.

Our data on frusemide agree with those in the literature. Although frusemide acts predominantly by inhibiting sodium reabsorption in the ascending limb of Henle's loop, an inhibitory effect on proximal tubular sodium transport has also been demonstrated (Puschett, 1981; Brenner *et al.*, 1969). This latter effect could be the result of the carbonic anhydrase inhibitory action of frusemide (Puschett & Goldberg, 1968). This combined action on the proximal tubule and Henle's loop may explain why CH_2O did not change in our study. Lithium clearance was increased by frusemide, in agreement with the observation of Steele *et al.* (1975). This inhibitory effect of frusemide on lithium reabsorption could be the result of the above mentioned action of frusemide on proximal tubular sodium reabsorption.

Because of the inter-individual variability of changes after frusemide administration and the possible differences in gastro-intestinal absorption it is difficult to compare precisely the effects of nifedipine and frusemide. Therefore, we have

analyzed the data, using values from the period of the maximal natriuretic effect in each volunteer (Table 2). When we compare the effects of nifedipine and frusemide on free water clearance it becomes clear that the drugs must have different sites of action. The increase in free water clearance after nifedipine administration favours a predominantly proximal site of action. Frusemide did not change free water clearance, which can be explained by a combined action on the proximal tubule and Henle's loop. In view of the differences between nifedipine and frusemide found with free water clearance technique, we would have expected to find a greater increase in lithium excretion after administration of nifedipine if lithium is only reabsorbed in the proximal tubule. Since we did not find differences in lithium excretion after nifedipine and frusemide administration, we feel that our data suggest that lithium is reabsorbed to an important degree in Henle's loop, a possibility also indicated by rat studies (Steele *et al.*, 1976). Lithium clearance *per se* may, therefore, be an imperfect marker of proximal tubular sodium reabsorption. From an ongoing study we have indications that the increase

in lithium excretion corrected for the increase of sodium excretion may be a better marker in this respect. Indeed, when the ratio FeLi/FeNa was used to compare maximal nifedipine and frusemide effects in this study a significant difference became apparent (respectively 4.1 ± 0.4 and 2.9 ± 0.3 ; $P < 0.05$).

In conclusion, we have demonstrated a clear diuretic and natriuretic effect of nifedipine in healthy volunteers. The increase of both free water clearance and lithium clearance favours a predominantly proximal site of action. As potassium excretion remained unchanged nifedipine must also interfere with $\text{Na}^+ - \text{K}^+$ exchange in the distal tubule. Free water clearance but not lithium clearance allowed us to differentiate between nifedipine and frusemide effects. The reliability of lithium as a marker of proximal tubular sodium reabsorption deserves further investigation.

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Appendix

Formula used in calculations:

$$\text{Clearance } y = \frac{U_y \cdot V}{P_y}$$

U_y : concentration of substance y in urine

P_y : concentration of substance y in plasma

Fractional proximal sodium reabsorption (fPRNa^+):

$$\text{fPRNa}^+ = 100 - \frac{U_{\text{Na}^+ + \text{K}^+} \cdot V}{\text{ECCxP}_{\text{Na}^+}} \times 100\% - \frac{\text{CH}_2\text{O}}{\text{ECC}} \times 100\%$$

Fractional distal sodium reabsorption (fDRNa^+) corrected for total tubular load (ECCxNa^+):

$$\text{fDRNa}^+ (\text{ECCxNa}^+) = \frac{\text{CH}_2\text{OxP}_{\text{Na}^+} + V \cdot U_{\text{K}^+}}{\text{ECC} \times P_{\text{Na}^+}} \times 100\%$$

Fractional distal sodium reabsorption corrected for distal tubular load (VxNa^+):

$$\text{fDRNa}^+ (\text{VxNa}^+) = \frac{\text{CH}_2\text{OxP}_{\text{Na}^+} + V \cdot U_{\text{K}^+}}{\text{VxP}_{\text{Na}^+}} \times 100\%$$

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