The natriuresis following oral administration of the calcium antagonists—nifedipine and nitrendipine

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1 Ten healthy individuals received in random order placebo, nifedipine 10 mg, nifedipine 20 mg, nitrendipine 10 mg and nitrendipine 20 mg as single oral administrations at weekly intervals. On the day before each treatment placebo was administered. Urine was collected for 6 h and then for 18 h after each administration.

2 There was a significant increase in urine volume and sodium excretion after the drugs, but no change in potassium excretion. The effect was most evident in the 6 h after drug administration. The effect was no greater at the higher doses of either drug.

3 A natriuretic-diuretic action of nifedipine and nitrendipine has been confirmed in man. The mechanism of the effect remains unclear.

Keywords natriuresis nifedipine nitrendipine

Introduction

Nifedipine is a calcium channel blocker used in the treatment of ischaemic heart disease and hypertension (Murphy et al., 1983). Nitrendipine is a new drug of this group which has been shown to inhibit transmembrane Ca\(^{2+}\)-induced contraction of smooth muscle cells and to increase the blood flow in the coronary and other vascular beds in animals (Stoepel et al., 1981; Kazda et al., 1983). It exerts an antihypertensive effect which is related to arteriolar dilatation associated with a reflex increase in heart rate and cardiac index (Ventura et al., 1982). Clinical trials indicate that nitrendipine is effective and is well tolerated in the dose range of 10 mg to 30 mg per day (Burris et al., 1982; Andren et al., 1982).

Whilst ankle oedema and fluid retention have been recorded in clinical trials of nifedipine (Terry, 1982; Pedersen et al., 1980) there have been reports of a natriuresis following administration of the drug. Klutsch et al. (1972) found a brief diuresis in nine hypertensive patients following the intravenous administration of 1 mg nifedipine. Leonetti et al. (1982) reported that 10 mg nifedipine orally induced a marked increase in urine volume and renal sodium excretion in hypertensive patients but induced little change in normotensives. Verapamil had no effect. Yokoyama & Kaburagi (1983) reported a diuresis in both normotensive and hypertensive subjects with and without chronic glomerulonephritis during an intravenous infusion of nifedipine. However Soto et al. (1981) were unable to detect a natriuresis after oral administration of 20 mg nifedipine and Valdes et al. (1982) found that urine volume increased following this dose only when the hypertensives were taking a high sodium diet.

A natriuretic effect of nitrendipine has been reported in rats (Garthoff et al., 1982) and in a group of eight male patients with hypertension (Sambhi et al., 1984). Other calcium antagonists which have been reported to cause natriuresis are nicardipine (Van Schaik et al., 1984) and felodipine (Edgar et al., 1984).

The aim of the present study was to establish whether or not a significant natriuretic effect of
nifedipine and nitrendipine could be demonstrated in healthy man. We also wanted to compare the effects of the two drugs at similar doses and to gain some insight into the dose response relationship for the effect.

Methods

Eleven healthy drug-free subjects (six male) aged between 18 and 24 years were recruited but one subsequently withdrew. The study protocol had been approved by the Ethics Committee of Bristol and Weston Health Authority. The study consisted of five treatment periods at weekly intervals. There were three consecutive days to each treatment period during which no ethanol, tea, coffee or smoking were permitted. The diet for each participant was standardised and normal sleeping time maintained throughout each treatment period. No observations were made or drugs taken on the first day. On the second day placebo was administered and on the third the subjects received in random order either nifedipine 10 mg or 20 mg, nitrendipine 10 mg or 20 mg or placebo. A double dummy technique was employed and the study was conducted double blind. All drugs were administered at 08.00 h and subjects remained indoors for the 6 h following drug administration. On the second and third day of each treatment period urine was collected from 08.00 h to 14.00 h and a separate collection was made from 14.00 h to 08.00 h the following morning. Volumes were recorded and aliquots were frozen for subsequent measurement of sodium, potassium and creatinine. A full blood count and plasma urea and electrolytes and liver function tests were performed on all the subjects prior to entry and at the end of the complete study.

Statistical analysis

Analysis of variance was applied to the measurements on the initial day of placebo administration to test for variability in baseline between treatment periods. Once comparability of baseline readings had been established analysis of variance was applied to the measurements on the second day of drug administration for each of the five treatment periods. Subsequently Student’s $t$-test for paired data was used to assess the significance of changes from baseline due to the individual drugs. A probability of less than 0.05 has been taken as significant throughout the analysis.

Results

There were no abnormalities in the haematological or plasma biochemical tests performed before or after the study. One female subject experienced headache, flushing, dizziness, nausea, tremulousness and tachycardia (140 beats/min) after the administration of nifedipine 10 mg during the second treatment period. She withdrew from the study and is not included in the presented data. Headache was experienced commonly in the hours after drug administration as follows: nifedipine 10 mg five occasions, nifedipine 20 mg seven occasions, nitrendipine 10 mg four occasions, nitrendipine 20 mg five occasions and placebo two occasions. Headaches were also experienced on eight of the pretreatment days when placebo only was administered. Flushing and feelings of faintness occurred on nine occasions in relation to administration of active drugs and on one occasion after placebo.

Creatinine excretion

There were no significant differences in the daily excretion of creatinine on days of drug or placebo administration.

Urine volume

In the collections during the 6 h after initial placebo administration in each study period there was no significant difference ($F = 0.97$). There was a significant difference between the 6 h collections on the treatment days ($F = 5.0; P < 0.005$). The mean urine volume was greater than the previous day’s value after all the active treatments (see Figure 1). The mean increases in 6 h urine volume (± s.e. mean) were 180 ± 79 ml ($P < 0.05$) for nifedipine 10 mg, 54 ± 59 ml (NS) for nifedipine 20 mg, 129 ± 40 ml ($P < 0.01$) for nitrendipine 10 mg, 189 ± 73 ml ($P < 0.05$) for nitrendipine 20 mg and −80 ± 47 ml (NS) for placebo. The urine volume was no higher after nitrendipine 20 mg than after nitrendipine 10 mg and the volume after nifedipine 20 mg was significantly less than that after nifedipine 10 mg ($P = 0.01$).

In the 24 h period after initial placebo administration in each study period there was no significant difference ($F = 0.1$). Comparison of the treatment days by analysis of variance revealed border-line significance ($F = 2.4; P = 0.07$). Only after nifedipine 10 mg was the 24 h urine volume significantly higher than that on the previous day of placebo administration.
Natriuresis with nifedipine and nitrendipine

**Sodium excretion**

In the collections during the 6 h after initial placebo administration in each study period there was no significant difference ($F = 0.5$). Comparison of the 6 h collections on the treatment days only revealed borderline significance ($F = 2.53; P = 0.057$). Comparison of sodium excretion in all the 6 h collections was statistically significant ($F = 2.1; P < 0.05$). Mean 6 h sodium excretion was greater than the previous day's value after all the active treatments (Figure 2). The mean increases in 6 h sodium excretion were 20 ± 9 mmol ($P = 0.052$) for nifedipine 10 mg, 10 ± 7 mmol (NS) for nifedipine 20 mg, 16 ± 5 mmol ($P < 0.02$) for nitrendipine 10 mg, 16 ± 8 mmol (NS) for nitrendipine 20 mg and −3 ± 7 mmol (NS) for placebo. The sodium excretion was similar in magnitude after nitrendipine 10 mg and 20 mg and was less after nifedipine 20 mg than after nifedipine 10 mg ($P < 0.05$).

In the 24 h period after initial placebo administration in each study period there was no significant difference ($F = 0.2$). Comparison of the values on the treatment days showed that the differences did not reach statistical significance ($F = 2.0; P = 0.1$). Only after nifedipine 10 mg was the 24 h sodium excretion significantly higher than that on the previous day of placebo administration.

**Potassium excretion**

There was no difference in the 6 h or 24 h potassium excretions during the days of placebo administration ($F = 0.7$ and 0.1 respectively). There was no difference in the 6 h or 24 h potassium excretions on the days of drug administration ($F = 0.7$ and 0.8 respectively). There was no change in the potassium excretion in the 6 h or 24 h periods following any drug compared to that on the previous day of placebo administration.

**Discussion**

Although the results of the study do not provide clear-cut statistical proof for each of the treatments the overall conclusion that the first administration of nifedipine and nitrendipine causes a modest diuretic and natriuretic effect is inescapable.

![Figure 1](image_url)
able. The dose-response relationship for the effect appears to be flat for nifedipine with 10 mg producing maximum diuresis. The data suggest that increasing the dose of nifedipine beyond 10 mg may actually reduce the effect.

The results of this study are in keeping with those of others performed before and concurrently with this work. The body of evidence points clearly to the existence of a diuretic action of some of the calcium antagonists. However the mechanism by which this effect arises remains uncertain. Nifedipine has been found to cause an increase in glomerular filtration rate (Yokoyama & Kaburagi, 1983; Klutsch et al., 1972) in man but this has not been a consistent finding either in man (Leonetti et al., 1982; Christensen et al., 1982) or animals (Marre et al., 1982). In itself a change in glomerular filtration rate would not be expected to cause a diuresis in the presence of normal renal function. More significant would be the reported increase in renal plasma flow with a concomitant fall in filtration fraction (Marre et al., 1982) but when renal blood flow has been measured in man the increases have usually been minimal (Christensen et al., 1982) or transient (Klutsch et al., 1972) or similar in magnitude to the change in glomerular filtration rate (Yokoyama & Kaburagi 1983). Consequently Leonetti et al. (1982) and Yokoyama & Kaburagi (1983) concluded that the natriuretic action of nifedipine could not be due entirely to the increase in glomerular filtration or renal blood flow. Sambhi et al. (1984) drew a similar conclusion for nitrendipine from a study in which glomerular filtration rate and renal blood flow increased non-significantly but free water clearance and osmolar clearance were elevated after one week's treatment. From a study of nicardipine Van Schaik et al. (1984) concluded that the increase in sodium excretion caused by the drug was due to a rise in glomerular filtration rate and decreased proximal and distal tubular sodium reabsorption.

The notable feature in the present study was the tendency for the diuretic effect to decrease with the higher doses of the drugs. It is tempting to speculate that a specific effect on the renal tubule evident at the lower doses may have been partly offset by haemodynamic changes at the higher dose.

Whether this pharmacological action of the calcium antagonists has any therapeutic implica-
tion remains an open question. However it may help to explain some of the differences between this group of drugs and other vasodilators — namely the fall in plasma potassium concentrations (Murphy et al., 1983; Pedersen et al., 1980) and the low incidence of fluid retention and tendency for a decrease in body weight with prolonged treatment (Pedersen et al., 1980). It is possible that increases in foot volume observed in the absence of changes in body weight (Murphy et al., 1983) could be explained by vascular dilatation rather than salt and water retention.

References


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