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# Renal and hemodynamic responses to bumetanide in hypertension: Effects of nitrendipine

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**Renal and hemodynamic responses to bumetanide in hypertension: Effects of nitrendipine.** The effects of a calcium antagonist on the response to a loop diuretic were tested in eight hypertensive patients while they received 120 mmol · 24 $hr^{-1}$ of dietary Na. Nitrendipine (N; 20 mg) or placebo (P) was administered twice daily for five days and bumetanide (B; 1 mg, i.v.) for the last three days of each period. Cardiac index (CI) was measured during tilt. B alone significantly ($P < 0.05$; $N = 7$) reduced CI and increased total peripheral resistance; N prevented these effects of B. Neither drug altered BP consistently. Although three days of B increased plasma renin activity (PRA) during P and N, it increased plasma aldosterone ($P_{Aldo}$) only during P (P, 4.4 ± 1.3 to 7.6 ± 1.0; $P < 0.05$. N, 5.7 ± 1.3 to 6.0 ± 1.3; pg · $liter^{-1}$; NS). B increased Na excretion without changing GFR or RPF; this was followed by 18 hours of decreased renal Na excretion. These actions were unchanged by N. N did not change the cumulative excretion of B (P, 268 ± 35 vs. N, 217 ± 21 μg) or the relationship between Na excretion and the log of B excretion. However, Na excretion was increased ($P < 0.05$) by 40 to 60% in the six hour period following the first two doses of N. Therefore, the cumulative Na balance was more negative during five days of N (P, −47 ± 17 vs. N, −108 ± 24 mmol; $P < 0.05$). The effect of N and B on Na balance were independent. In conclusion, short-term administration of N: 1) increases CI and reduces TPRI in the post-diuretic state; 2) blunts B-induced increase in $P_{Aldo}$ without modifying the rise in PRA; 3) does not change B kinetics or dynamics or the post-diuretic period of renal Na retention; 4) causes negative Na balance which is additive with that produced by B.

Calcium antagonists and diuretics are used with increasing frequency to treat patients with hypertension or coronary artery disease. However, there is little quantitative information about how these drugs interact. Studies of their antihypertensive interaction have produced conflicting results. Sever and Poulter [1] demonstrated that a thiazide produced a further fall in the BP of hypertensive subjects receiving a calcium antagonist. In contrast, Cappuccio et al [2] found no significant change and most other trials have shown either no additional effect or a less than additive action [2–4]. The basis for this apparently unfavorable interaction in the treatment of hypertension has not yet been established. Since both classes of drugs are natriuretic [5–8], it has been suggested that the antagonistic effect in hypertension might be explained if calcium antagonists blocked the salt-depleting actions of diuretics [4]. Alternatively, calcium antagonists might modify diuretic kinetics. Moreover, a stable BP might conceal important additional effects of these drugs on cardiac output or total peripheral resistance. Thus, loop diuretics given to patients with cardiac failure can stimulate the renin-angiotensin system sufficiently to raise the peripheral vascular resistance and BP [9]. Since calcium antagonists can blunt angiotensin-induced pressor responses [10, 11], they might also blunt these potentially adverse hemodynamic effects of diuretics. Therefore, this study was designed to investigate the interaction between these two classes of drugs in further detail. We examined the effects of a calcium antagonist (nitrendipine) on the salt-depleting and hemodynamic actions of a loop diuretic (bumetanide) in hypertensive subjects. Measurements were also made of key hormones and drug kinetics to explore further potential mechanisms of interaction.

Previous studies of the "diuretic braking phenomenon" [12] have shown that during liberal salt intake, progressive Na depletion induced by a loop diuretic is curtailed by a reduction in Na excretion in the post-diuretic period. In contrast, during severe dietary salt restriction, it is curtailed by a decreased natriuretic response to the diuretic [13–15]. This post-diuretic salt retention limits the efficacy of diuretics and persists despite blockade of angiotensin II formation or alpha$_1$-adrenoreceptors. Therefore we investigated whether a calcium antagonist modified this phenomenon.

## Methods

Studies were performed on seven men and one woman aged 45 to 65 years. All drugs were withdrawn one month prior to the study. Entry criteria included: a diastolic blood pressure (DBP) of 95 to 109 mm Hg on two separate occasions measured in the clinic two to four weeks after withdrawal of antihypertensive drugs; a diagnosis of essential hypertension; normal values for hemogram, blood urea and electrolytes, blood sugar, and urinalysis. Patients with only mild hypertension were selected to obviate the effects of an abrupt fall in BP produced by the calcium antagonist on changes in hemodynamics or Na balance. The study was passed by the Institutional Review Board of the University of Florida and VA Medical Center. All subjects gave informed consent.

Patients were admitted to the Clinical Research Center Metabolic Balance Ward for 14 days. They received a regulated diet with weighed quantities of food which provided 20 mmol · 24

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$hr^{-1}$ of Na, 70 mmol · 24 $hr^{-1}$ of potassium (K) and 1.1 g · $kg^{-1}$ · 24 $hr^{-1}$ of protein. This was supplemented with 6 g · 24 $hr^{-1}$ of NaCl given in equal quantities with breakfast (7 a.m.), lunch (12 midday) and dinner (6 p.m.). Therefore, the daily intake of Na was 120 mmol. Water was provided ad libitum. Subjects refrained from smoking or drinking alcohol.

After an initial two-day washout period, for the next five days subjects received either 20 mg of nitrendipine (Baypress; Miles Pharmaceuticals, West Haven, Connecticut, USA) at 6 a.m. and 6 p.m., or matching placebo. Thereafter, there was a second two-day washout period after which they were crossed over to receive the other agent (nitrendipine or placebo). Allocation to receive nitrendipine or placebo first was by random number (4 received nitrendipine first and 4 received placebo). The study was conducted under double-blind conditions. At 9 a.m. on the last three days of each week the patients also received a daily intravenous injection of 1 mg of bumetanide (Bumex; Hoffmann-LaRoche, Inc., Nutley, New Jersey, USA).

Urine was collected each six hours beginning at 6 a.m. on the third day of each week. At 8 a.m., the patients were seated quietly for two minutes while blood pressure (BP) was measured by a sphygmomanometer and heart rate (HR) was recorded.

Standard two-dimensional and pulsed Doppler echocardiograms [16] were performed at 11:30 a.m. on day 6 of each week; this was 2-1/2 hours after the second daily dose of bumetanide. The subjects were positioned at a 60° incline on a tilt table for 30 minutes before making the measurements. With the subject lying in the left lateral supine position, chamber dimensions, left ventricular wall thickness, ejection fraction and cardiac output were measured. The mean arterial pressure (MAP; diastolic plus 1/3 pulse pressure) and HR were recorded simultaneously. The fifth Korotkoff sound was used for diastolic BP. The total peripheral resistance index (TPRI) was calculated from MAP and cardiac index (CI). Seven of the subjects were also studied under the same conditions of diet and tilt before and 2-1/2 hours after administration of bumetanide (1 mg i.v.) alone to establish the effects of the diuretic itself.

On days 5 and 7 of each week, the renal responses to intravenous bumetanide were studied. With the subjects seated, a vein was cannulated in each forearm for intravenous infusion and blood sampling. At 6 a.m., the patients received 350 ml of water by mouth and a light breakfast. An intravenous infusion of dextrose solution (5 g · 100 $ml^{-1}$) containing [$^{99m}$Tc]-diethylenetriaminepentaacetic acid (DTPA; 0.013 $\mu$Ci · $kg^{-1}$ · $min^{-1}$; Metaphysics, Inc., Richmond, California, USA) and sodium paraaminohippurate (PAH; 0.20 mg · $kg^{-1}$ · $min^{-1}$; Merck, Sharp and Dohme, West Point, Pennsylvania, USA) was delivered at 1 ml · $min^{-1}$. Loading doses of 1.0 $\mu$Ci · $kg^{-1}$ DTPA and 8.8 mg · $kg^{-1}$ PAH were administered at the beginning of the infusion. After one hour for equilibration, there was a two hour basal clearance period. Thereafter bumetanide (1 mg; Bumex, Hoffman LaRoche, Inc.) was given as an intravenous bolus over two minutes. There followed five 30-minute clearance periods; blood was sampled at the midpoints of each. Samples for plasma renin activity (PRA) and plasma aldosterone concentration ($P_{Aldo}$) were drawn before the first dose and 150 minutes after the last dose of bumetanide.

Routine chemical methods have been described [13–15]. The PRA was estimated from the quantity of angiotensin I generated over a 90 minute incubation at 25°C (Travenol-Genetech Diagnostics, Cambridge, Massachusetts, USA). The $P_{Aldo}$ was estimated using a radioimmunoassay (Diagnostic Products Corp., Los Angeles, California, USA). Blood for assay of total catecholamine concentration ($P_{Cat}$) was drawn into tubes containing EGTA and glutathione and maintained on ice. Plasma was assayed using a radioenzymic method (Amersham Biomedical Research, Arlington Heights, Illinois, USA) for measurement of total catecholamines. All plasma samples for hormone assay were stored at −70°C.

A high-pressure liquid chromatographic (HPLC) method for quantitation of bumetanide in urine was developed from a prior method to maximize the sensitivity, shorten the sample preparation time and decrease instrumentation requirements [17]. After addition of the 4-benzyl bumetanide derivative as an internal standard (supplied by LaRoche Pharmaceuticals) urine was extracted once with ethyl acetate at an acidic pH, separated, evaporated to dryness, reconstituted with methanol, and chromatographed using a reversed-phase, C-18, radial-compression cartridge with fluorescence detection. Sensitivity limits were approximately 1 ng · $ml^{-1}$ of bumetanide in urine, with a coefficient of variation for identical urine samples not exceeding 4% [17].

The glomerular filtration rate (GFR) was estimated from DTPA clearance and the renal plasma flow (RPF) from Hippuran clearance. The fractional excretion of sodium ($FE_{Na}$) was calculated by dividing the urine-to-plasma concentrations of Na by DTPA.

Results were assessed by paired *t*-tests comparing bumetanide-induced changes during nitrendipine and placebo periods. The values were considered statistically significant at $P < 0.05$ [18]. An analysis of variance (ANOVA) with repeated measures was used to assess the effects of nitrendipine and days of diuretic administration on bumetanide excretion, and the effects of nitrendipine and bumetanide on cumulative Na balance.

## Results

All subjects completed the protocol. One complained of headache during nitrendipine but there were no other adverse effects. All subjects had DBP's above 95 mm Hg on two separate occasions in the clinic. However, under conditions of regulated dietary intake in hospital, three subjects had DBP's that were only 90 to 95 mm Hg.

The hemodynamic effects of bumetanide alone were investigated in seven subjects studied under the same conditions of head-up tilt before and 2-1/2 hours after bumetanide (1 mg i.v.). Although bumetanide did not change the MAP (112 ± 5 to 112 ± 5 mm Hg), the HR was increased (81 ± 2 to 97 ± 4; $P < 0.01$), the CI was reduced (2.32 ± 0.20 to 1.69 ± 0.12; $P < 0.01$) and TPRI was increased (2,690 ± 315 to 3,812 ± 420 dynes · $sec^{-1}$ · $cm^{-5}$; $P < 0.05$). Figure 1 shows hemodynamic data obtained during 60° head-up tilt 2-1/2 hours after bumetanide plus placebo compared to a similar time after bumetanide plus nitrendipine. Nitrendipine reduced the MAP of seven of eight subjects in the post-diuretic state, although the overall change was not statistically significant. However, the HR and CI were consistently increased by nitrendipine and the TPRI was reduced. Therefore, the maintenance of BP after nitrendipine was accomplished by a greater cardiac output but at a sharply

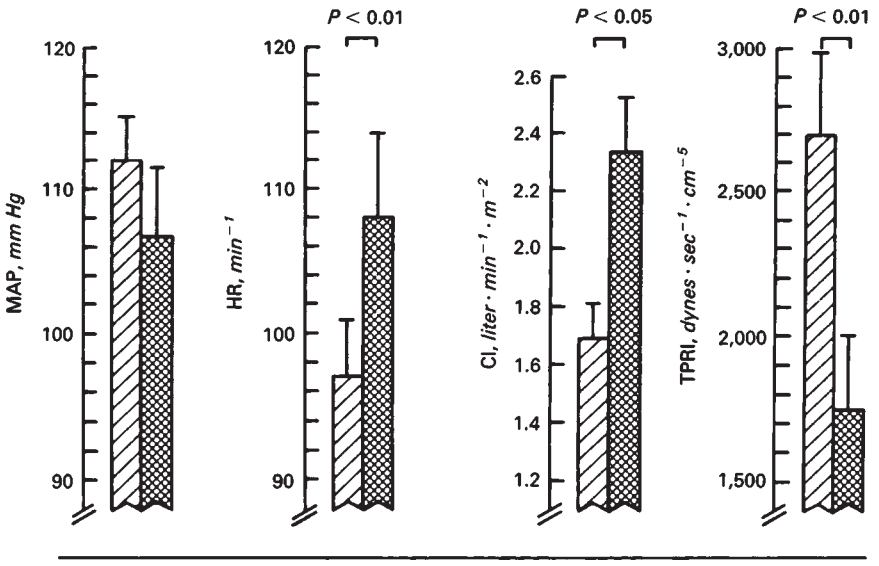


**Fig. 1.** *Mean ± SEM values for heart rate, mean blood pressure, cardiac index and total peripheral resistance index.* Measurements were made 5-1/2 hours after placebo (diagonal shading) or nitrendipine (cross-hatched shading). Subjects had received bumetanide 2-1/2 hrs previously and were tilted 60 degrees upright for 20 min before measurements were made.

**Table 1.** Plasma total catecholamines, renin activity and aldosterone concentration with bumetanide: Effects of nitrendipine

| | Placebo | | Nitrendipine | |
|---|---|---|---|---|
| | Before | After B | Before | After B |
| $P_{Cat}$ $pg \cdot ml^{-1}$ | 310 ± 35 | 480 ± 90[a] | 520 ± 75[b] | 670 ± 105[ab] |
| PRA $ngAI \cdot ml^{-1} \cdot hr^{-1}$ | 6.5 ± 2.4 | 12.3 ± 3.3[a] | 5.3 ± 2.1 | 15.5 ± 3.8[a] |
| $P_{Aldo}$ $ng \cdot dl^{-1}$ | 4.4 ± 1.3 | 7.6 ± 1.0[a] | 5.7 ± 1.3 | 6.0 ± 1.3 |

Mean ± SEM values ($N = 8$) for data obtained before the first dose of bumetanide (before) and 2-1/2 hr after the third dose (after B).
[a] $P < 0.05$ comparing before and after bumetanide
[b] $P < 0.05$ comparing placebo and nitrendipine periods

**Table 2.** Mean blood pressure, Na excretion and renal hemodynamics with bumetanide: Effects of nitrendipine

| | Placebo | | Nitrendipine | |
|---|---|---|---|---|
| Days | B1 | B3 | B1 | B3 |
| MAP *mm Hg* | | | | |
| Basal | 180.0 ± 3.3 | 103.1 ± 3.3 | 102.4 ± 1.7 | 99.5 ± 3.1 |
| Bumetanide | 109.4 ± 3.7 | 105.8 ± 3.9 | 100.7 ± 3.6 | 101.4 ± 3.4 |
| Change with B | +1.4 ± 1.2 | +2.7 ± 1.0 | −1.7 ± 2.5 | +1.9 ± 1.7 |
| $U_{Na}V$ $\mu mol \cdot min^{-1}$ | | | | |
| Basal | 117 ± 22 | 59 ± 8 | 167 ± 44 | 82 ± 12 |
| Bumetanide | 820 ± 59 | 633 ± 47 | 741 ± 65 | 638 ± 41 |
| Change with B | +703 ± 50 | +574 ± 46 | +574 ± 68 | +556 ± 39 |
| GFR $ml \cdot min^{-1}$ | | | | |
| Basal | 84 ± 7 | 83 ± 6 | 88 ± 9 | 82 ± 8 |
| Bumetanide | 86 ± 8 | 81 ± 5 | 80 ± 4 | 90 ± 9 |
| Change with B | +2 ± 11 | −1 ± 6 | −8 ± 10 | +8 ± 11 |
| RPF $ml \cdot min^{-1}$ | | | | |
| Basal | 386 ± 25 | 346 ± 30 | 390 ± 47 | 370 ± 37 |
| Bumetanide | 410 ± 38 | 353 ± 27 | 374 ± 26 | 415 ± 39 |
| Change with B | +24 ± 52 | +7 ± 28 | −16 ± 41 | +45 ± 48 |

Mean ± SEM values ($N = 8$). Data were obtained over 2 hr before and 2-1/2 hr following bumetanide (1 mg). Patients received placebo or nitrendipine (20 mg) before starting the basal measurements. B1 and B3 refer to the first and third days of bumetanide administration. There were no significant effects of nitrendipine on the changes produced by bumetanide. However, basal $U_{Na}V$ was higher ($P > 0.05$) on days B1 and B3 with nitrendipine compared to placebo.

reduced total peripheral resistance. Nitrendipine effectively prevented the fall in cardiac output and rise in peripheral resistance induced by the diuretic alone.

The values for $P_{Cat}$ were higher during nitrendipine than placebo (Table 1). Comparison of hormone measurements made in the basal state before bumetanide administration with values obtained 150 minutes after the third bumetanide injection demonstrated a consistent increase in $P_{Cat}$ and PRA during placebo and nitrendipine administration. Whereas $P_{Aldo}$ also increased consistently with bumetanide during placebo, this change was not seen during nitrendipine administration.

In the basal state before the daily bumetanide injection, the MAP again tended to be 4 to 9 mm Hg lower during nitrendipine than placebo, although these differences were not statistically significant. Table 2 shows data before and 2-1/2 hours after bumetanide. Two patterns were apparent in the basal $U_{Na}V$. First, nitrendipine increased the basal $U_{Na}V$, as shown by higher values ($P < 0.05$) compared to placebo on both the first and third days of bumetanide (B1 and B3). Second, the basal $U_{Na}V$ was reduced ($P < 0.02$) on days B3 compared to B1 during both the placebo and nitrendipine periods. There were no associated changes in the basal values of GFR or RPF. Bumetanide caused a sharp increase in $U_{Na}V$ without consistent effects on GFR or RPF; these responses were unaltered by nitrendipine. Moreover, examination of the time course of changes from the 30-minute urine collection also failed to disclose any effects of nitrendipine.

The cumulative excretion of bumetanide averaged 19% of the injected dose over the first 2-1/2 hours and 24% over 24 hours (Table 3). This was unaffected by nitrendipine and was not different between the first and third doses of bumetanide. An analysis of variance with repeated measures demonstrated no significant effects of nitrendipine or days of bumetanide administration on bumetanide excretion over 2-1/2 or 24 hours (F values below 1; NS).

The increase in fractional Na excretion ($FE_{Na}$) was related to

**Table 3.** Cumulative excretion of bumetanide (μg)

| | Placebo | Nitrendipine |
|---|---|---|
| Day 1 of bumetanide | | |
| First 2-1/2 hr | 205 ± 29 | 181 ± 19 |
| 24 hr | 265 ± 36 | 220 ± 21 |
| Day 3 of bumetanide | | |
| First 2-1/2 hr | 184 ± 22 | 198 ± 25 |
| 24 hr | 230 ± 22 | 262 ± 31 |

Mean ± SEM values ($N$ = 8) for cumulative renal excretion of unchanged bumetanide. Data are shown for the first 2-1/2 hr and the entire 24 hr after injection of 1 mg of bumetanide. There were no significant effects of nitrendipine.

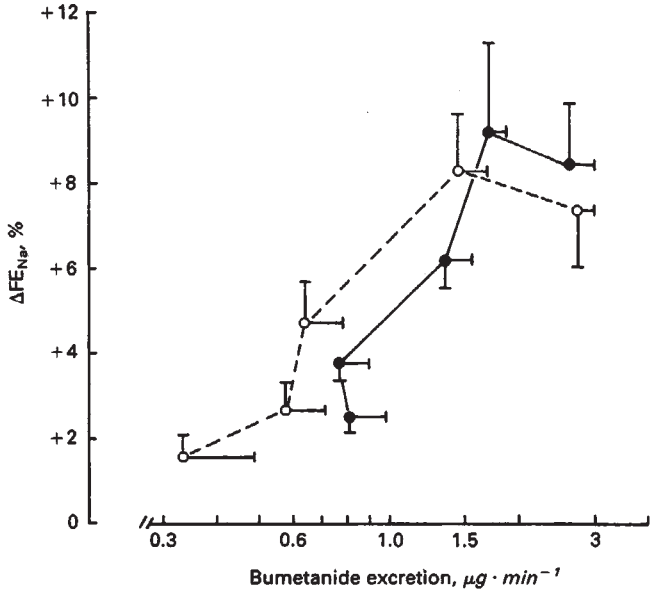


**Fig. 2.** *Mean ± SEM values for increases in fractional excretion of sodium as a function of renal bumetanide excretion (log scale).* Data are shown for five 30 min periods following the first intravenous dose of bumetanide given during placebo (○) or nitrendipine (●).

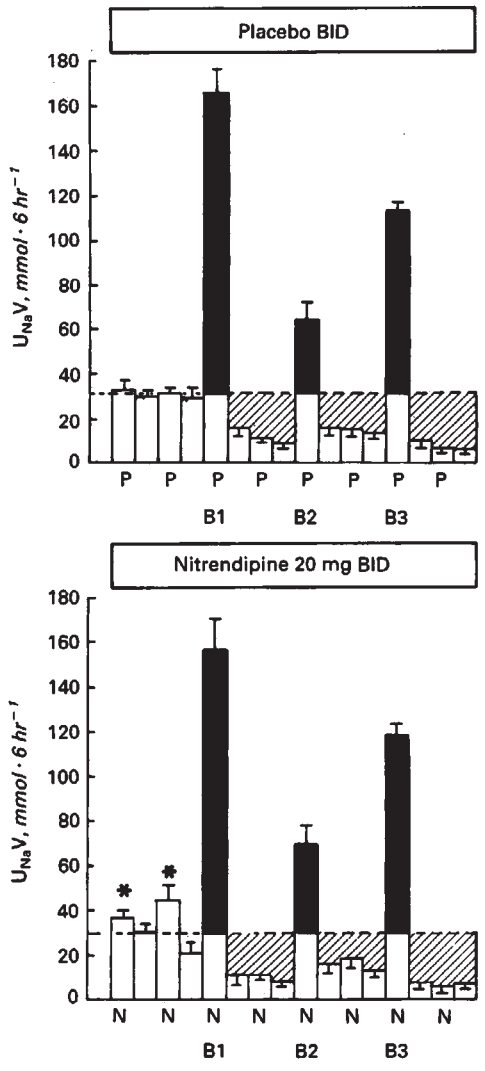


**Fig. 3.** *Mean ± SEM values for 6-hourly renal sodium excretion during administration of placebo or nitrendipine.* Data are shown as the mean of two pre-diuretic 24 hr periods, and for the 3 days on which bumetanide was given (B1, B2, and B3). The level of Na intake is indicated by the broken horizontal line. Negative Na balance is indicated by solid shading and positive Na balance by diagonal shading. *$P < 0.05$ comparing nitrendipine and placebo periods.

the rate of bumetanide excretion (log scale, Fig. 2). The maximal effect (responsiveness) was not changed by nitrendipine, nor was there any consistent change in the intercept of the linear part of the relationship (sensitivity).

Before bumetanide, $U_{Na}V$ was 40 to 60% higher in the two six-hour periods following nitrendipine administration than the corresponding periods during placebo (Fig. 3). This natriuretic effect was less evident on the second day of nitrendipine administration. Bumetanide increased $U_{Na}V$ substantially on each day leading to a negative Na balance in the six hours after the diuretic (indicated by solid shading, Fig. 3). However, during the subsequent 18 hours, $U_{Na}V$ was reduced well below the level of intake resulting in a positive Na balance during this period (indicated by diagonal shading in Fig. 3). The patterns of bumetanide-induced natriuresis followed by renal Na conservation were quite comparable during placebo and nitrendipine administration. As in previous studies [19], $U_KV$ followed a similar pattern of diuretic-induced loss followed by renal retention of K and was not affected by nitrendipine (data not shown).

During placebo administration, the balance for Na was not significantly different from zero before bumetanide administration (Fig. 4). The nitrendipine-induced natriuresis led to a modest negative Na balance; by the end of the first day of nitrendipine administration, Na balance was 45 ± 18 mmol more negative during nitrendipine than placebo ($P < 0.05$). Natriuresis was more variable on the second day of nitrendipine administration and differences in cumulative Na balances were not statistically significant. The first dose of bumetanide produced a negative Na balance which was similar during both placebo and nitrendipine phases and was maintained over the subsequent three days. The 45 mmol of Na loss induced by the first dose of nitrendipine persisted throughout the period of diuretic administration; on the last day of bumetanide, Na balance was 61 ± 25 mmol ($P < 0.05$) more negative during nitrendipine than placebo. An ANOVA demonstrated signifi-

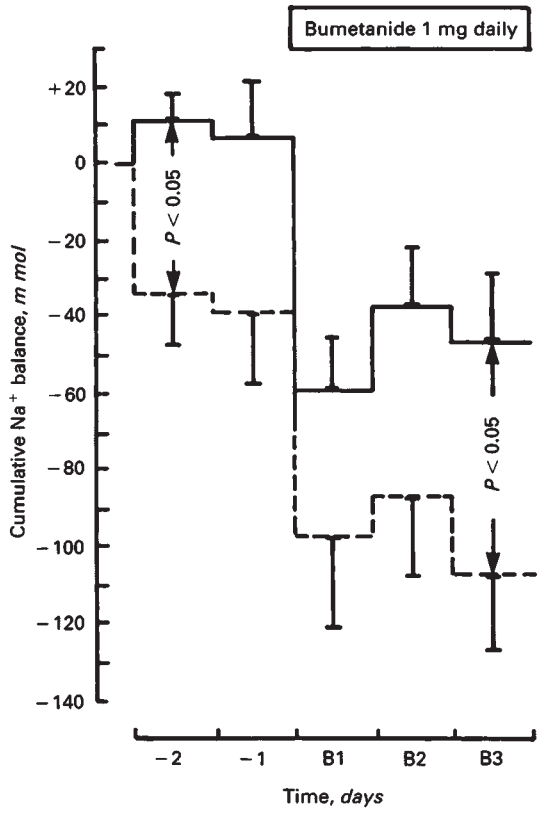


**Fig. 4.** *Mean ± SEM values for cumulative 24 hr Na balance during placebo (solid lines) and nitrendipine administration (broken lines).* Data are shown for 2 days before and 3 days during bumetanide administration (B1, B2, and B3).

cant ($P < 0.05$) effects of nitrendipine and bumetanide on Na balance, but no interaction between them (F = 0.7; NS).

## Discussion

The main new findings of this study were that in patients with mild hypertension nitrendipine, given during orthostatic stress and in the post-diuretic state, increased the cardiac output and reduced the peripheral resistance. This reversed the hemodynamic effects produced by the diuretic itself. Nitrendipine interrupted bumetanide-induced increases in $P_{Aldo}$ without modifying the stimulation of PRA or $P_{Cat}$. Bumetanide dynamics and kinetics were not perturbed by nitrendipine. Over a five day period, an initial Na loss induced by nitrendipine was additive with that produced by bumetanide.

During the first few days of thiazide treatment for hypertension, there is a fall in cardiac output and a rise in peripheral resistance, although this effect wanes during prolonged therapy [20]. Our results show a similar early hemodynamic response to a loop diuretic. Intravenous doses of loop diuretics given for cardiac failure can also reduce CI because of an abrupt rise in TPRI [9]. This adverse hemodynamic response, which limits the therapeutic use of loop diuretics in this setting, has been attributed to activation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system [9]. Calcium antagonists can prevent the rise in vascular resistance in response to infusions of angiotensin II [10, 11] vasopressin, catecholamines [21, 22] or reflex activation of the sympathetic nervous system [23]. In mild hypertension, calcium antagonists alone have little effect on CI or TPRI during rest, although they can cause marked increases in CI and vasodilation during reflex stimulation produced by exercise [24]. Therefore, calcium antagonists might prevent the adverse increase in peripheral resistance caused by loop diuretics, although this has not been investigated previously. The present study was undertaken during orthostatic stress to activate the neural and humeral mechanisms fully. The increases in $P_{Cat}$ and PRA produced by bumetanide confirmed that these systems were indeed activated by the diuretic. Nitrendipine reversed not only the sharp rise in peripheral resistance produced by the diuretic, but also the fall in cardiac output consistent with blockade of activated peripheral vasoconstrictor mechanisms. Of interest was the finding that the MAP following the diuretic was similar during the placebo and nitrendipine periods, despite widely different values for cardiac output and peripheral resistance (Fig. 1). Therefore, important hemodynamic interaction between these two classes of drugs can occur that may not be appreciated by measurement of BP alone, as in some previous studies [1–3]. It will be important to determine whether similar hemodynamic interactions are apparent during more prolonged administration of thiazides and calcium antagonists, since these classes of drugs are currently recommended as first-line treatment for hypertension [25].

In a previous study of patients with mild hypertension admitted to hospital [8], the antihypertensive response to nitrendipine was modest. In the present study, there was no significant effect of nitrendipine on MAP (Table 2). This may relate to the relatively young age, somewhat restricted level of dietary salt intake and to the mild degree of hypertension of our subjects. Thus, the antihypertensive response to calcium antagonists has been reported in some studies to vary directly with age, dietary salt intake and ambient BP [26–28]. Moreover, the full antihypertensive response to nitrendipine can take up to three weeks to develop [29].

Calcium antagonists blunt the rise in aldosterone secretion provoked by infusion of angiotensin II [10]. This may explain the interruption of diuretic-induced increases in $P_{Aldo}$ by nitrendipine which occurred despite a sharp increase in PRA. Hyperaldosteronism can contribute to the adverse effects of long-term diuretic therapy on serum potassium concentration and metabolic alkalosis [30]. Therefore, a moderation of diuretic-induced hyperaldosteronism by calcium antagonists could be beneficial. Indeed, a blunting of angiotensin II-induced pressor responses and aldosterone secretion has been shown in hypertensive subjects during established verapamil therapy [31].

The first dose of a calcium antagonist given to patients with established hypertension usually increases RPF [32]. During prolonged therapy, persistent increases in RPF are seen in some studies [33] whereas others report a return to baseline values [6]. The absence of a consistent rise in GFR or RPF with nitrendipine in this study may relate to the timing of the study after the third dose of the drug or to the mild degree of hypertension, since these drugs have little effect on renal hemodynamics at normal levels of BP [7, 34]. Moreover, increases in RPF are more pronounced in hypertensive patients with reductions in GFR below 80 ml/min [34]. Alternatively, there may be a heterogeneity of renal vascular responses to

calcium antagonists in hypertension, analogous to the "modulator" and "non-modulator" responses to angiotensin II infusion [35]. The study population of eight patients was too small to allow subset analysis of the responses to nitrendipine.

In the present study, the natriuretic action of the calcium antagonist was evident as a 40 to 60% increase in renal Na excretion in the six hour periods following the first two doses, and a 25 to 40% increase during the basal periods on the experimental days. The nitrendipine natriuresis on the experimental days was not accompanied by consistent increases in GFR and therefore reflects a decreased tubular Na reabsorption. Micropuncture studies in rats have demonstrated that calcium antagonists can decrease tubular fluid and Na reabsorption in the proximal [36] and distal tubules [37], but do not alter reabsorption in the loop of Henle [36, 38]. Therefore, calcium antagonists and loop diuretics have distinct sites of action in the kidney which is consistent with our finding that they have independent salt-depleting actions.

Net loss of Na during diuretic administration is the outcome of a short-term natriuresis which is followed by a post-diuretic period of Na conservation [13–15]. Since nitrendipine did not modify either of these processes, it did not interrupt the diuretic-induced negative Na balance. Indeed, the modest loss of Na during the first day of nitrendipine administration (45 mmol, compared to the placebo period) was simply additive with the loss of 54 mmol produced by three days of bumetanide administration. At the end of the five days of nitrendipine administration, the net Na loss with nitrendipine was 61 mmol greater than during placebo, which is comparable to the net loss of 103 mmol of Na over eight days reported for hypertension subjects given nitrendipine alone [8]. In neither study were there consistent effects on K excretion. These results of short-term studies do not support the suggestion that calcium antagonists may interrupt diuretic-induced salt loss [4].

In conclusion, the present short-term study in hypertensive subjects has highlighted several points of interaction between loop diuretics and calcium antagonists which may have clinical significance. Thus, during orthostatic stress, nitrendipine can reverse the increase in peripheral resistance and reduction in cardiac output provoked by a loop diuretic. This may be valuable, especially in patients with impaired cardiac reserve in whom a fall in output may have adverse consequences. Interruption of diuretic-induced aldosterone secretion, if sustained during prolonged therapy, could counter some adverse effects of diuretics attributed to hyperaldosteronism. Finally, nitrendipine and bumetanide had additive Na-depleting actions during modest dietary salt restriction.

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