# A Double-Blind Study of the Blood Pressure Lowering Effect of a Thiazide Diuretic in Hypertensive Patients Already on Nifedipine and a Beta-Blocker

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Twelve hypertensive patients who were already on treatment with atenolol (100 mg once daily) and nifedipine as tablets (20 mg twice daily) were entered into a double-blind, randomized crossover study of the addition of 1 month's treatment with either bendrofluazide (5 mg once daily) or a matching placebo.

The addition of bendrofluazide to the combination of atenolol and nifedipine did not cause any statistically significant fall in the blood pressure 2 h after the last dose of nifedipine compared to treatment with placebo [bendrofluazide: 135.2 ± 5.1/89.8 ± 2.5 (mean ± s.e.), versus placebo: 132.1 ± 4.6/89.9 ± 3.1 mmHg; $P$ = NS]. However, 12 hours after the last dose of nifedipine blood pressure tended to be lower whilst on bendrofluazide compared with placebo.

Plasma urate levels were significantly higher on the diuretic compared to placebo (461 ± 27 versus 396 ± 21 μmol $P < 0.001$). Plasma potassium was lower on the diuretic compared to placebo (3.59 ± 0.12 vs 3.76 ± 0.10) but this difference just failed to reach statistical significance.

The results of this study suggest that a thiazide diuretic has little additive effect on blood pressure in patients already on treatment with atenolol and nifedipine, particularly when nifedipine is maximally effective. However, the addition of a diuretic does have potentially deleterious metabolic effects.

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## Introduction

Thiazide diuretics have been used in the treatment of essential hypertension as first step therapy for a long time [1] despite their undesirable and sometimes serious side-effects [2,3]. However, they are still widely used in the long-term treatment of high blood pressure, often in combination with a β-blocker [4,5].

Nifedipine is an effective blood pressure lowering agent on its own and in combination with a β-blocker [6]. Circumstantial evidence suggests that sodium balance may be related in some way to the activity of calcium entry antagonists; for instance, a high sodium diet, instead of lessening the acute effect of nifedipine, appears to enhance it [7–9].

Diuretics on their own may not have an additive effect on blood pressure in patients already on nifedipine [10–12], although contrasting results have also been reported recently, either using different protocols [13,14] or highly selected hypertensive patients [15].

It has also been shown that the addition of nifedipine to the treatment of patients already on combination therapy with β-blockers and diuretics causes an additional fall in blood pressure [4], but it is not yet clear whether the diuretic was necessary in this combined treatment.

We therefore conducted a double-blind randomized crossover study to investigate the effect of the addition of a thiazide diuretic to the treatment of patients with essential hypertension who were already on atenolol and nifedipine.

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## Patients and methods

Patients with essential hypertension, referred to the Blood Pressure Unit by local general practitioners, were included in the study if no underlying cause for their high blood pressure had been found. Patients with renal failure, ischaemic heart disease or cerebrovascular disease, pregnancy, diabetes mellitus, gout, hypokalaemia from any cause or who were taking the oral contraceptive pill were excluded from the study. Twelve patients who gave their informed consent entered and completed the study. There were eight men and four women; three were white and nine were black. The mean age was 51 years (range 40–65 years). All patients were already on nifedipine tablets (Adalat retard; 20 mg twice daily) and atenolol (100 mg daily) and had been on the two drugs for at least 1 month before entry to the study. The average period on atenolol was 1.6 months (range 1–5 months) and on nifedipine, 9 months (range 1–26 months). All patients continued with nifedipine and atenolol for a further month, observations being made every 2 weeks. Average supine blood pressure on atenolol and nifedipine at entry to the study was 140/94 mmHg, approximately 2 h after the morning dose; blood pressure measurements were made 2 and 12 h after taking the last dose. At the end of this 1-month period, blood pressure (2 and 12 h after the last dose), pulse rate and weight were measured. The patients were then entered into a double-blind, randomized crossover study to investigate the effects of the addition of bendrofluazide (5 mg once daily in the morning) for 1 month and matching placebo for a further month. Patients continued on their usual diet and did not alter it during the study. Five patients were started on bendrofluazide and seven on placebo. During the trial patients were seen every fortnight in the Blood Pressure Unit at 0900–1000 h, approximately 12 h after their evening dose of nifedipine, when their blood pressure, heart rate and weight were measured. They then took their usual atenolol and nifedipine therapy with either bendrofluazide or placebo and measurements were made 2 h after that dose. Each patient was seen on the same day of the week, at the same time of the day, by the same nurse and in the same room. Blood pressure was measured in the same arm by nurses using semi-automatic ultrasound sphygmomanometers (Arteriosonde 1225, Roche) [16] with attached recorders. Measurements were therefore free from observer bias. Supine and standing blood pressures were the means of five readings taken every 1 or 2 min. Pulse rate was measured by a pulse monitor (Cambridge 3048). At each visit patients were also asked how they felt and volunteered side-effects were recorded. Blood was taken for estimation of urea, creatinine, electrolytes, uric acid, phosphate, total calcium and glucose before randomization and at the end of each period. Blood samples for measuring plasma renin activity, plasma aldosterone and plasma nifedipine levels were also taken 2 and 12 h after the nifedipine dose. Blood samples were taken without stasis after the patient had been sitting upright for 10 min between 1000 and 1200 h. Plasma renin activity and plasma aldosterone were measured by radio-immunoassay [17,18]. Plasma nifedipine levels were analysed using gas liquid chromatography [19].

## Statistical analysis

Mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. All results are recorded as mean ± s.e.m. Student's t-tests for paired observations were carried out using the University of London's computer and the North Western Universities' Statistical Package for Social Sciences. The study had a power of 90% to detect a 7.6-mmHg change in mean arterial pressure at the 5% level of significance [20].

## Results

There was no significant difference in blood pressure between pre-randomization and placebo periods (Table 1). After 4 weeks of addition of bendrofluazide to the combination of atenolol and nifedipine there were no

**Table 1.** Blood pressure, heart rate and weight before and during treatment with either placebo or bendrofluazide in 12 hypertensive patients already on nifedipine and atenolol.

| | | | Placebo | | Bendrofluazide | |
|---|---|---|---|---|---|---|
| | 2 h | 12 h | 2 h | 12 h | 2 h | 12 h |
| Supine SBP (mmHg) | 140.3 ± 3.2 | 159.7 ± 3.8** | 132.1 ± 4.6 | 156.7 ± 5.4** | 135.2 ± 5.1 | 154.7 ± 7.1** |
| Supine DBP (mmHg) | 94.2 ± 2.4 | 106.9 ± 2.4** | 89.9 ± 3.1 | 104.1 ± 2.4* | 89.8 ± 2.5 | 98.5 ± 2.8* |
| Standing SBP (mmHg) | 132.2 ± 3.5 | 150.6 ± 3.2** | 127.8 ± 3.9 | 151.1 ± 3.8** | 124.8 ± 4.5 | 144.8 ± 6.3** |
| Standing DBP (mmHg) | 95.0 ± 3.3 | 107.9 ± 1.9** | 92.9 ± 3.0 | 105.9 ± 3.0* | 88.2 ± 2.6 | 103.0 ± 2.3** |
| Supine pulse (beats/min) | 64.1 ± 2.3 | 63.5 ± 2.2 | 62.8 ± 1.7 | 62.7 ± 2.2 | 65.8 ± 1.6 | 63.0 ± 1.8 |
| Standing pulse (beats/min) | 68.2 ± 3.2 | 69.2 ± 3.1 | 66.7 ± 2.4 | 69.1 ± 2.6 | 67.8 ± 1.6 | 67.7 ± 2.6 |
| Weight (kg) | | 87.0 ± 4.6 | | 86.7 ± 4.4 | | 87.2 ± 4.5 |

Results are means ± s.e.m. *$P < 0.005$, **$P < 0.001$ for differences with the corresponding treatment 2 h after the last dose of nifedipine. SBP, systolic blood pressure; DBP, diastolic blood pressure.

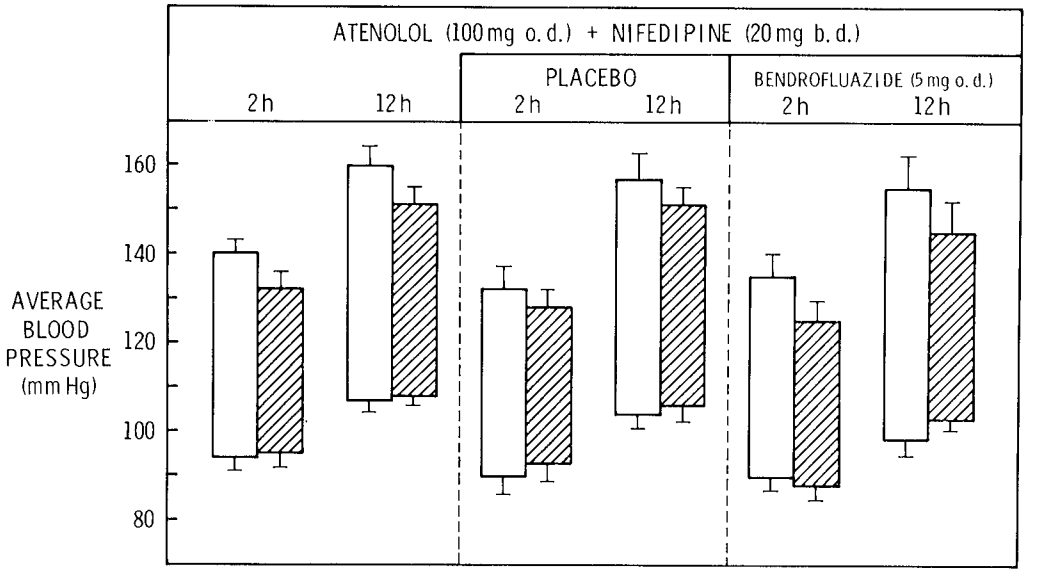


**Fig. 1.** Supine (□) and standing (▨) systolic and diastolic blood pressures 2 and 12 h after the last dose of nifedipine during treatment with placebo and bendrofluazide. Results are mean ± s.e.m; $P < 0.001$ for differences between the 2- and 12-h blood pressure levels.

significant changes in supine systolic or diastolic blood pressures either at 2 or 12 h after nifedipine, compared to equivalent blood pressures measured after 1 month of placebo (Fig. 1). Standing blood pressures, however, were lower, though not significantly, while on the diuretic compared to placebo (Table 1). Also, when time had elapsed since the last dose of nifedipine (i.e. 12 h), blood pressure was lower while on the diuretic although the differences were not statistically significant (Table 1).

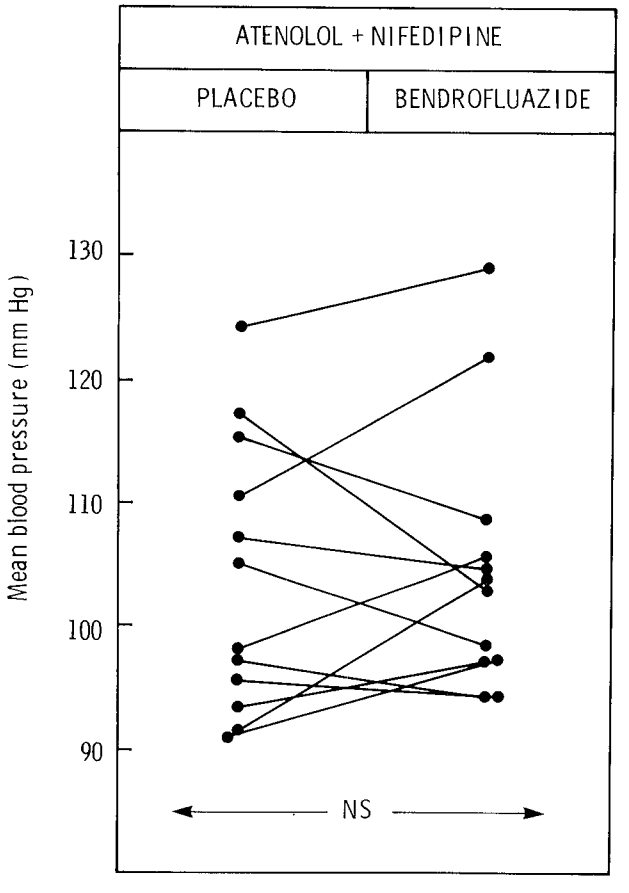


**Fig. 2.** Changes in mean supine blood pressure 2 h after the last dose of nifedipine between week 4 of treatment with placebo and with bendrofluazide.

Six patients showed a decrease in mean supine blood pressure 2 h after the last dose when week 4 of diuretic treatment was compared to week 4 of placebo; whereas six patients showed an increase in blood pressure (Fig. 2). This difference in response to the diuretic was not related to the order of treatment, age, race, sex or changes in plasma renin activity. Before the randomization, eight patients had a supine mean blood pressure above 105 mmHg; five of them showed a decrease in blood pressure while on the diuretic, whereas three showed an increase (Fig. 2). Out of the four patients whose supine mean blood pressures were below 105 mmHg before randomization, one showed a decrease in blood pressure on the diuretic and three showed an increase (Fig. 2). It is therefore unlikely that the blood pressure response to the diuretic was related to the degree of blood pressure control whilst on combination therapy with a β-blocker and nifedipine in the present study. Heart rate and body weight did not change during the study (Table 1).

Blood pressures measured at 12 h after the last dose of nifedipine throughout the study were significantly higher than at 2 h (Fig. 1) and plasma nifedipine levels were significantly lower 12 h after the last dose compared to those measured after 2 h on each treatment (Table 2). Bendrofluazide added to the combined treatment did not induce any change in the nifedipine levels, either at 2 or at 12 h compared with placebo treatment. No significant changes were observed in plasma renin activity and plasma aldosterone throughout the study (Table 2). Uric

acid significantly increased during treatment with bendrofluazide as compared with placebo ($P < 0.001$; Table 2) and a decrease in plasma potassium which just failed to reach statistical significance occurred in the same period. No significant changes were observed among the other measured variables (Table 2). All patients who entered the trial completed it without any adverse effects.

## Discussion

This double-blind randomized crossover study demonstrates that the addition of a thiazide diuretic in the treatment of hypertensive patients who are already on a β-blocker and on nifedipine has little additive effect on blood pressure over a month when nifedipine is maximally effective. This finding is similar to that found when a thiazide diuretic is added to nifedipine alone [10–12]. Nifedipine has been shown to have an additive effect on blood pressure when combined with a β-blocker [21–24]. Beta-blockers have also been shown to potentiate the antihypertensive action of a diuretic [5] and this action has been attributed, at least in part, to the inhibition by the β-blocker of the compensatory rise in renin release caused by the diuretic [25].

However, our study suggests that in the presence of nifedipine, the effect of a thiazide diuretic on blood pressure is lessened. Indeed, when time had elapsed since the last dose of nifedipine (i.e. 12 h after the last dose) and when plasma nifedipine levels were accordingly reduced, blood pressure levels whilst on bendrofluazide were lower, though not significantly so, compared to the corresponding values on placebo (Table 1). This suggests that when nifedipine is maximally effective [26], the thiazide diuretic has little or no effect on blood pressure, whereas 12 h after the last dose, when nifedipine is less effective [26], the diuretic may then become more effective. The majority of patients in the present study were black. The antihypertensive action of diuretics tends to be greater in black hypertensive patients, partly due to a less reactive renin system. Therefore, the lack of an additive effect of a thiazide added to nifedipine and a β-blocker in these patients, if anything, adds further weight to our negative findings.

Our results are also supported by two previous studies showing that when nifedipine is given to patients who are already on a thiazide diuretic, a significant additional fall in blood pressure is seen, whereas when patients are already on treatment with nifedipine, the addition of a diuretic does not induce a further significant fall in blood pressure when nifedipine is maximally effective [11,12]. However, other studies [13–15] have shown an additive effect of a diuretic added to nifedipine alone. In these studies the time of the blood pressure measurement in relation to the last dose of nifedipine is not given. Since nifedipine, even as a tablet has a relatively short length of action [26], it is difficult to be certain that blood pressure was measured when nifedipine was maximally effective.

The mechanism by which nifedipine may lessen the blood pressure lowering effect of the thiazide diuretic is not known. Nifedipine is known to cause a natriuresis in the short term [27–30] and in the longer term this reduction in sodium balance is maintained [12] and could, therefore, block any further natriuretic effect of

**Table 2.** Plasma renin activity, aldosterone, nifedipine levels and biochemistry before and during treatment with either placebo or bendrofluazide in 12 hypertensive patients already on nifedipine and atenolol.

| | | | Placebo | | Bendrofluazide | |
|---|---|---|---|---|---|---|
| | 2 h | 12 h | 2 h | 12 h | 2 h | 12 h |
| Plasma renin activity (ng/ml per h) | 0.40 ± 0.19 | 0.25 ± 0.08 | 0.32 ± 0.11 | 0.25 ± 0.05 | 0.93 ± 0.55 | 0.47 ± 0.18 |
| Plasma aldosterone (pmol/l) | 310 ± 30 | 323 ± 55 | 215 ± 27 | 237 ± 26 | 289 ± 60 | 261 ± 27 |
| Plasma nifedipine (ng/ml) | 38.1 ± 7.6 | 14.6 ± 3.1** | 53.5 ± 9.4 | 14.8 ± 3.6*** | 44.6 ± 6.0 | 9.9 ± 2.0*** |
| Plasma sodium (mmol/l) | | 139.3 ± 0.6 | | 140.5 ± 0.8 | | 140.2 ± 0.6 |
| Plasma potassium (mmol/l) | | 3.95 ± 0.16 | | 3.76 ± 0.10 | | 3.59 ± 0.12† |
| Plasma urea (mmol/l) | | 6.9 ± 0.5 | | 6.5 ± 0.3 | | 6.8 ± 0.5 |
| Plasma creatinine (μmol/l) | | 110.8 ± 6.4 | | 109.2 ± 6.2 | | 108.3 ± 7.8 |
| Plasma uric acid (μmol/l) | | 394 ± 28 | | 396 ± 21 | | 461 ± 27*‡ |
| Plasma calcium (mmol/l) | | 2.37 ± 0.02 | | 2.34 ± 0.03 | | 2.36 ± 0.02 |
| Plasma phosphate (mmol/l) | | 1.01 ± 0.05 | | 0.97 ± 0.04 | | 0.93 ± 0.04 |
| Plasma glucose (mmol/l) | | 4.87 ± 0.18 | | 5.09 ± 0.23 | | 5.22 ± 0.48 |

Results are means ± s.e.m. *$P < 0.001$ for difference with placebo. **$P < 0.005$, ***$P < 0.001$ for differences with the corresponding treatment 2 h after the last dose of nifedipine. †$P < 0.005$, ‡$P < 0.001$ for differences with pretreatment.

the diuretic. Alternatively, it is possible that nifedipine blocks the mechanism in arteriolar smooth muscle that is responsible for the fall in blood pressure with the diuretic [7].

Despite the lack of change in blood pressure with the addition of the thiazide diuretic there was a reduction in plasma potassium which just failed to reach statistical significance and a significant increase in uric acid levels (Table 2). These metabolic side-effects of thiazide diuretics have been known for a long time [2,3] as have the longer-term effects on lipids [31] and blood sugars [32]. The MRC Trial [33] demonstrated the problems arising from the long-term use of thiazide diuretics and has also shown up the increased frequency of impotence and ventricular ectopic beats in the group treated with diuretics [34] as was shown previously in a smaller group of patients [35].

In conclusion, our results, if confirmed in larger numbers of patients with high blood pressure, could have important therapeutic implications. The suggestion is that, in hypertensive patients who are already on treatment with a β-blocker and nifedipine, there may be little to gain overall by the addition of a thiazide diuretic.

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