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A Double-Blind Crossover Study of the Effect of Concomitant Diuretic Therapy in Hypertensive Patients Treated With Amlodipine

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Twelve patients with essential hypertension who were already on treatment with the long-acting calcium antagonist amlodipine (5 mg once daily) were entered into a double-blind, randomized crossover study of the addition of one month's treatment with either bendrofluazide (5 mg once daily) or matching placebo.

The addition of bendrofluazide did not cause any statistically significant fall in the supine blood pressure compared to treatment with placebo (147.6/90.1 ± 4.8/2.8 *v* 150.8/92.6 ± 4.3/2.3 mm Hg, respectively).

Plasma potassium was significantly lower on bendrofluazide as compared to placebo (3.11 ± 0.14 *v* 3.62v ± 0.13 mmol/L, $P < .001$) and 10 of 12 patients had a fall in plasma potassium while on diuretic.

The results of this study suggest that a thiazide diuretic has little additive effect on blood pressure in patients already on the long-acting dihydropyridine amlodipine, and may cause hypokalemia. Am J Hypertens 1991;4:297–302

KEY WORDS: **Amlodipine, thiazides, blood pressure.**

Both thiazide diuretics and calcium antagonists are widely used in the treatment of essential hypertension.[1,2] However, contrasting results have been reported as to whether thiazide diuretics have an additive effect on blood pressure in patients already taking a calcium antagonist[3–14] and the issue has been the subject of recent debate.[15–17]

A relatively new dihydropyridine calcium antagonist, amlodipine, has been shown to effectively lower blood pressure in patients with essential hypertension[18,19] and to be a long-acting calcium antagonist[18] with a long elimination half-life.[20] 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 amlodipine.

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 (serum creatinine > 150 μmol/L), ischemic heart disease or cerebrovascular disease, pregnancy, diabetes mellitus, or who were taking oral contraceptives were excluded from the study. Twelve patients who gave their informed consent entered and completed the study. They had been seen regularly every 2 to 4 weeks at least 2 months before entry to the study and had either received no previous treatment or, if they had, it was stopped at least 2 weeks before the study. Diuretics were stopped at least 8 weeks before the study. They were then included in the study if, after a further month of observation on no treatment, their supine dia-

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stolic pressure was ≥95 mm Hg. All patients were studied taking their normal diet and no dietary advice was otherwise given. There were 7 men and 5 women; 9 were white and 3 were black. The mean age was 55 years (range 44 to 63 years). Average supine blood pressure after 1 month of observation on no treatment was 173/105 mm Hg. Patients were then started on amlodipine tablets (5 mg daily given in the morning) and they were kept on this treatment throughout the study. After 4 weeks of observation on amlodipine alone patients were entered into a double-blind randomized crossover study to investigate the effect of the addition of bendrofluazide (5 mg daily given in the morning) for a month and matching placebos for a further month while on amlodipine as above. 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 between 9 and 10 AM, approximately 24 h after their morning dose of amlodipine and bendrofluazide or matching placebo, and their blood pressure, heart rate, and weight were measured. Each patient was seen on the same day of the week, at the same time of day, by the same nurse, in the same room. Blood pressure was measured in the same arm by nurses using semiautomatic ultrasound sphygmomanometers (Arteriosonde 1225, Roche, Nutley, NJ)[21] with attached recorders. Measurements were therefore free from observer bias. Supine and standing blood pressures were the means of 5 readings taken every 1 to 2 min. Pulse rate was measured by 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, total calcium, and glucose at baseline, before randomization and at the end of each treatment period. Blood samples for measuring plasma renin activity, plasma aldosterone, and plasma atrial natriuretic peptides were also taken at the end of each period. Blood samples were taken without stasis after the patient had been sitting upright for at least 10 min between 10 AM and 12 noon. Plasma renin activity, plasma aldosterone, and plasma ANP were measured by radioimmunoassay.[22-24] Mean arterial pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure. All results are recorded as mean ± SEM and 95% confidence intervals (CI).[25] Student's *t* tests for paired observations were carried out using the University of London computer and the Northwestern Universities Statistical Package for Social Sciences. The study had a power of 90% to detect a 7.5 mm Hg change in mean arterial pressure at the 5% level of significance.[26]

RESULTS

There was no significant difference in blood pressure between pre-randomization and placebo periods (Table

TABLE I. BLOOD PRESSURE, HEART RATE, AND BODY WEIGHT AT BASELINE, DURING TREATMENT WITH AMLODIPINE ALONE, AND WITH EITHER AMLODIPINE AND BENDROFLUAZIDE OR AMLODIPINE AND MATCHING PLACEBO IN 12 PATIENTS WITH ESSENTIAL HYPERTENSION

		Amlodipine (5 mg) once daily					
		Alone		Bendrofluazide (5 mg daily)		Placebo	
Variables	Baseline	Week 2	Week 4	Week 2	Week 4	Week 2	Week 4
Supine Blood Pressure (mm Hg)							
Systolic	172.8	158.1†	150.7‡	148.1	147.6	151.0	150.8
	(4.1)	(5.3)	(4.9)	(4.5)	(4.8)	(3.8)	(4.3)
Diastolic	105.2	96.7‡	93.2§	89.8	90.1	92.4	92.6
	(1.8)	(2.8)	(3.0)	(3.1)	(2.8)	(1.9)	(2.3)
Supine pulse	78.8	78.1	80.4	79.7	80.2	78.7	80.6
(beats per min)	(4.4)	(3.7)	(3.9)	(2.5)	(3.1)	(3.3)	(3.6)
Standing Blood Pressure (mm Hg)							
Systolic	166.0	155.9	147.6‡	137.8	141.4*	148.2	150.4
	(4.4)	(7.3)	(5.4)	(6.4)	(6.8)	(4.1)	(4.9)
Diastolic	109.6	99.3§	96.7§	92.2	92.8	95.9	95.7
	(1.7)	(2.7)	(2.7)	(3.5)	(2.9)	(2.7)	(3.4)
Standing pulse	87.6	85.9	87.2	89.1	86.7	86.8	86.4
(beats per min)	(3.8)	(3.9)	(3.8)	(3.0)	(3.7)	(3.8)	(3.2)
Body weight (kg)	78.0	78.2	78.3	79.1	78.2	78.1	78.5
	(3.9)	(4.3)	(4.1)	(3.9)	(4.0)	(4.1)	(4.0)

*$P < .05$ when compared to placebo; †$P < .05$; ‡$P < .01$; §$P < .001$ when compared to baseline.

Results are mean (SEM).

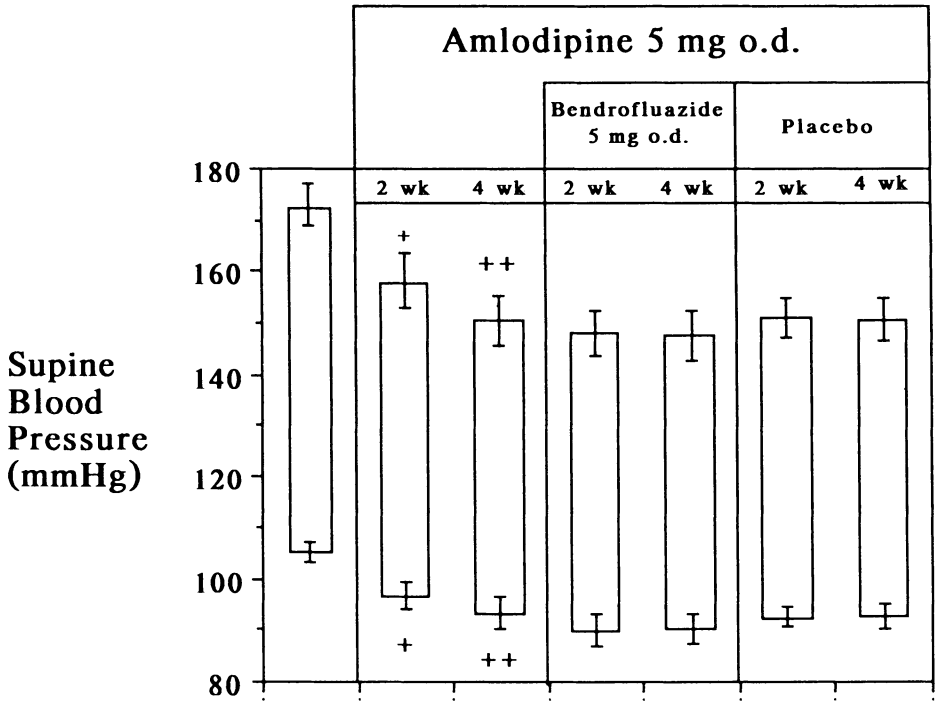

FIGURE 1. *Supine systolic and diastolic blood pressure at baseline, during treatment with amlodipine alone, and with either amlodipine and bendrofluazide or amlodipine and matching placebo in 12 patients with essential hypertension. Results are means ± SEM. + P < .01; ++ P < .001 when compared to baseline.*

1). When bendrofluazide was added to amlodipine there were no significant changes in either supine systolic or diastolic blood pressure at both 2 and 4 weeks as compared to the corresponding placebo value (Figure 1). Average supine blood pressure change was −3.2 mm Hg (95% confidence interval, −12.2 to 5.7 mm Hg) in systolic and −2.5 mm Hg (−7.3 to 2.3 mm Hg) in diastolic. However, standing blood pressure tended to be lower while on bendrofluazide as compared to placebo, the difference being statistically significant for the systolic blood pressure at the fourth week of treatment ($P < .05$) (Table 1). Average standing blood pressure change at 4 weeks was −9.0 mm Hg (−16.8 to −1.2 mm Hg) in systolic and −2.8 mm Hg (−9.1 to 3.4 mm Hg) in diastolic. Eight patients showed a decrease in mean supine blood pressure when the fourth week of diuretic treatment was compared to the fourth week of placebo treatment, whereas four patients showed an increase in mean supine blood pressure for the corresponding periods (Figure 2). This difference in response to the diuretic did not appear to be related to the order of treatment, age, race, or sex, nor was it related to the level of blood pressure before randomization. Heart rate and body weight did not change significantly throughout the study (Table 1). Plasma renin activity was significantly higher, as expected, during diuretic treatment as compared to placebo whereas plasma aldosterone and plasma ANP did not change significantly (Table 2). Plasma biochemistry showed a significant reduction in plasma potassium levels during bendrofluazide administration (Table 2). Ten of twelve patients had a decrease in plasma potassium levels, which, on average, was 0.50 mmol/L (95% confidence interval, −0.77 to −0.23 mmol/L) for the entire group. Along with this metabolic alteration there was also a significant reduction in plasma chloride and an increase in plasma urea, plasma creatinine, and plasma urate

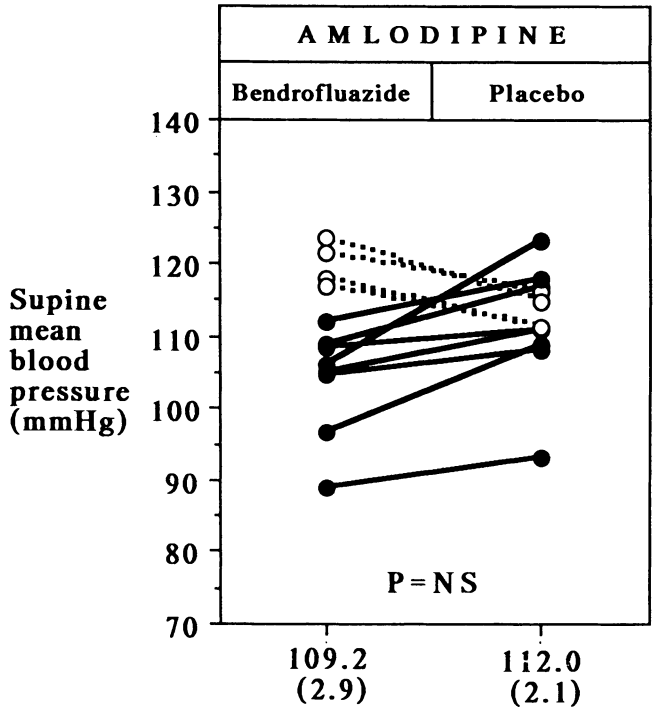

FIGURE 2. *Changes in mean supine blood pressure between 4 weeks of treatment with bendrofluazide and with placebo.*

TABLE 2. PLASMA RENIN ACTIVITY, ALDOSTERONE, ATRIAL NATRIURETIC PEPTIDE, AND BIOCHEMISTRY AT BASELINE, DURING TREATMENT WITH AMLODIPINE ALONE AND WITH EITHER AMLODIPINE AND BENDROFLUAZIDE OR AMLODIPINE AND MATCHING PLACEBO IN 12 PATIENTS WITH ESSENTIAL HYPERTENSION

		Amlodipine 5 mg daily		
Variables	Baseline	Alone	Bendrofluazide 5 mg daily	Placebo
Renin Activity(ng/mL/h)	1.71(0.34)	2.19(0.31)*	3.14(0.54)§	1.96(0.44)
Aldosterone(pmol/L)	557(52)	541(76)	469(41)	527(70)
ANP(pg/mL)	18.0(9.3)	12.1(7.7)**	14.4(11.6)	17.2(6.7)
Sodium (mmol/L)	139.2(0.5)	137.8(0.4)*	139.0(0.7)	139.8(0.5)
Potassium (mmol/L)	3.79(0.10)	3.70(0.14)	3.11(0.14)§	3.62(0.13)
Chloride (mmol/L)	106.7(0.7)	108.4(0.8)*	103.0(0.9)§	107.5(0.9)
Urea (mmol/L)	4.9(0.4)	5.1(0.3)	5.6(0.2)†	4.8(0.3)
Creatinine (μmol/L)	83.4(5.3)	78.2(4.9)	81.6(4.7)‡	76.9(4.2)
Urate (μmol/L)	332(19)	315(23)	390(33)‡	307(17)
Glucose (mmol/L)	5.4(0.3)	6.2(0.5)	6.5(0.7)	6.4(0.6)
T. Calcium (mmol/L)	2.31(0.03)	2.30(0.03)	2.33(0.02)	2.30(0.03)
Phosphate (mmol/L)	0.82(0.04)	0.75(0.05)	0.78(0.04)	0.79(0.05)
Protein (g/L)	75.7(1.7)	76.0(1.2)	76.2(1.5)	76.7(1.9)
Albumin (g/L)	41.7(0.9)	42.7(0.8)	43.1(0.8)	43.4(1.1)

*$P < .05$ and **$P < .001$ when compared to baseline.

‡$P < .05$; ‡$P < .01$; §$P < .001$ when compared to placebo.

Results are mean (SEM).

(Table 2). All patients who entered the trial completed it without any adverse effect.

DISCUSSION

This double-blind randomized crossover study demonstrates that the addition of a thiazide diuretic in the treatment of patients with essential hypertension who were already on the long-acting calcium antagonist, amlodipine, has little additive effect on blood pressure over a month. This finding is similar to that found when a thiazide diuretic is added to nifedipine alone[5,9] or combined with a β-blocker.[6] A controversy has arisen over the last few years, however, as to whether thiazide diuretics do have an additive effect on blood pressure in patients with essential hypertension who are on regular treatment with calcium antagonists,[3-14] with important clinical implications for the management of patients with high blood pressure.

There are several possible explanations for the discrepancies in the literature. In most studies the short-acting nifedipine has been employed, but in few of them was the blood pressure lowering effect related to the time elapsing after the administration of nifedipine. Studies in which the possible additive effect of a diuretic was evaluated when nifedipine was maximally effective were not able to show any additive effect of the thiazides, whereas studies where time-after-dose was not controlled claimed an additive effect of thiazide diuretics on blood pressure. As nifedipine is a short-acting drug, its major effect wearing off 4 to 6 h after administration,[27] the results reported in the literature are difficult to compare. With the availability of long-acting dihydropyridine calcium antagonists like amlodipine, which has a long duration of life of 40 to 60 h,[20] allowing once-a-day administration,[18] we could not detect a significant additive effect of thiazide diuretics to its treatment. It has been argued that many studies available in the literature on the issue are of insufficient size to statistically detect the difference in blood pressure between treatments or that their design cannot properly address the point.[28] In our study we had a 90% chance to detect a significant fall in mean arterial pressure of 7.5 mm Hg. On average, supine mean blood pressure during thiazide diuretics was 2.7 mm Hg lower than on placebo. This difference was not statistically significant and it cannot be ruled out that with a much larger group of patients (more than 100 patients) this difference would have been significant on statistical grounds. However, in our view, clinical trials should indicate whether a treatment is of any clinical benefit and this should be judged on clinical grounds. In designing the trial we felt that a 7.5 mm Hg fall in supine mean blood pressure would represent a real clinical benefit, whereas a 2.7 mm Hg fall would not be regarded as of major clinical importance. This is also in view of the substantial side effects of thiazide diuretics, as shown in most studies and clearly confirmed in the present study where, after 4 weeks of treatment with 5 mg of bendrofluazide, plasma potassium fell in 10 of 12 patients

bringing plasma potassium down, on average, from 3.6 to 3.1 mmol/L. Furthermore, a recent multicenter trial employing a larger number of patients and a factorial design did not show any benefit when a diuretic was added to nifedipine.[9] These findings strengthen the view that the addition of a thiazide diuretic does not improve the blood pressure control in those patients with essential hypertension currently treated with dihydropyridine calcium antagonists.

The mechanism whereby dihydropyridines may lessen or even blunt the blood pressure lowering effect of a diuretic is not known. Calcium antagonists, such as nifedipine, are known to cause a natriuresis in the short-term[29,30] and it is now established that they maintain their natriuretic effect in the longer-term.[31] This action might, in turn, block any further natriuretic effect of the diuretics. This may explain why the blood pressure-lowering effect of calcium antagonists is not blunted by a high sodium intake[32,33] and also why moderate sodium restriction does not produce an additional fall in blood pressure in patients who are already on treatment with nifedipine.[34]

In conclusion, our results using a long-acting dihydropyridine calcium antagonist, amlodipine, confirm that the addition of a thiazide diuretic to patients with essential hypertension already on calcium antagonists has little or no effect on blood pressure and that potentially dangerous hypokalemia[35] may occur in some patients.

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