CLINICAL RESEARCH

Lack of effect of beta-blocker on flat dose response to thiazide in hypertension: efficacy of low dose thiazide combined with beta-blocker

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Abstract

Increasing the dose of a thiazide diuretic used alone in patients with essential hypertension has little further effect on blood pressure but increases the deleterious metabolic consequences of the diuretic. The effect of a beta-blocker on this flat dose response is not known. In two randomised crossover studies the effect of 12·5 mg, 25 mg, and 50 mg hydrochlorothiazide combined with 400 mg acebutolol was assessed. The mean fall in supine blood pressure was about 15% and was the same whatever dose of thiazide was used with the beta-blocker. As the dose of hydrochlorothiazide was increased, however, there was evidence of increasing metabolic consequences of the diuretic. The study did not define the minimum dose of diuretic, and doses of hydrochlorothiazide lower than 12·5 mg might be as effective.

These results suggest that many patients who are being treated with a combination of a beta-blocker and a diuretic are receiving unnecessarily large amounts of the diuretic without benefit to their blood pressure and with adverse metabolic consequences.

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Introduction

When a thiazide diuretic is used alone to treat high blood pressure increasing the dosage has little further effect on lowering the pressure but does increase the deleterious metabolic consequences of the diuretic—for example, hypokalaemia.[1 2] This flat blood pressure response to the dose of diuretic has been shown with both competitive inhibitors of angiotensin II and converting enzyme inhibitors to be largely due to the increased renin release and thereby angiotensin II concentration, which maintains blood pressure in the face of the increased loss of sodium and water as the dose of diuretic is increased.[3 4] Inhibition of angiotensin converting enzyme abolishes the flat dose response to diuretics, resulting in a progressive fall in blood pressure as the dose of diuretic is increased, provided that the formation of angiotensin II is blocked.[5] Beta-blockade inhibits renin release[6] and causes circulating angiotensin II concentrations to be reduced by about half. Part of the additive action of a beta-blocker and a diuretic has been attributed to the inhibition by the beta-blocker of the compensatory rise in renin release caused by the diuretic. Beta-blockers, however, appear to inhibit only sympathetically mediated renin release, and increasing amounts of diuretic combined with a beta-blocker may still cause a progressive compensatory rise in renin release and thereby angiotensin II concentrations. This could result in a flat dose response to the diuretic even in the presence of a beta-blocker. We therefore studied in two randomised crossover studies the effects of different doses of hydrochlorothiazide (50 mg, 25 mg, 12·5 mg) given once a day with the beta-blocker acebutolol at a fixed amount of 400 mg once daily (and in one phase 200 mg acebutolol plus 12·5 mg hydrochlorothiazide once daily) in patients with mild to moderate essential hypertension.

Patients and methods

We studied 24 patients with mild to moderate essential hypertension who had been referred to the blood pressure unit by local general

practitioners. Any treatment designed to lower blood pressure was stopped at least two weeks before the study and any diuretics at least four weeks before the study. Patients were excluded if there was evidence of renal failure, ischaemic heart disease, or cerebrovascular disease or if they were taking oral contraceptives or other drugs. Informed consent was obtained from each patient. All drugs were given once daily in the morning. There were two separate studies. In the first study acebutolol 400 mg once daily and hydrochlorothiazide 25 mg once daily for one month were compared with acebutolol 400 mg once daily and hydrochlorothiazide 50 mg once daily for one month in a randomised crossover study. Twelve patients (seven men, five women) were included in this study; eight were white and four black. The mean age was 46 years (range (29-62) and the mean supine diastolic pressure 114 mm Hg (range 106-127 mm Hg). In the second study three different dose combinations were given for four weeks each, the order of administration being randomised. The three combinations were acebutolol 400 mg with hydrochlorothiazide 12·5 mg, acebutolol 400 mg with hydrochlorothiazide 25 mg, and acebutolol 200 mg with hydrochlorothiazide 12·5 mg. Twelve patients (six men, six women; six white, six black) were studied. The mean age was 49 years (range 40-64) and mean supine diastolic pressure 107 mm Hg (range 99-120 mm Hg). All patients were studied taking their normal diet, and no dietary advice was given.

The procedure in both studies was identical, except that in the second study after four weeks' treatment with acebutolol 200 mg and hydrochlorothiazide 12·5 mg daily blood pressure was also measured 24 hours after the final dose was taken. During the trial all patients were seen fortnightly in the blood pressure unit. 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)[7] with attached recorders. The measurements were therefore free from any observer bias. Supine and standing blood pressures were taken as the means of five readings taken at intervals of one to two minutes with the patients in the corresponding positions. Blood pressure after exercise was a single reading taken one minute after a standard period of treadmill exercise. Pulse rate was measured with a Cambridge 3048 pulse monitor. Weight was measured at each visit. Blood was taken for estimation of blood urea, electrolyte, creatinine, uric acid, and glucose concentrations and plasma renin activity before active treatment and at monthly intervals thereafter. Blood was taken without stasis after the patient had been sitting upright for five minutes between 10 am and 12 noon. Plasma renin activity was measured by radioimmunoassay.[8] At each visit patients were asked how they felt and any side effects volunteered were recorded. Mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. All results were recorded as means ± SEM. Statistical analysis was performed using a computer and the north eastern universities' statistical package for the social sciences.

Results

In the first study (fig 1) the mean supine blood pressure fell from 173/114 ± 3·8/1·9 mm Hg with no treatment to 144/98 ± 5·7/3·4 mm Hg after four weeks' treatment with acebutolol 400 mg and hydrochlorothiazide 50 mg and to 145/97 ± 6·1/4·2 mm Hg after four weeks' treatment with acebutolol 400 mg and hydrochlorothiazide 25 mg. These were reductions of 15·2% and 15·4% respectively compared with the pretreatment value and were highly significant ($p < 0·001$). In the second study (fig 2) mean supine blood pressure fell from 169/107 ± 5·6/1·9 mm Hg with no treatment to 140/93 ± 4·7/3·2 mm Hg after four weeks' treatment with acebutolol and hydrochlorothiazide 25 mg; this was a reduction of 15·1% ($p < 0·001$). After four weeks' treatment with acebutolol 400 mg and hydrochlorothiazide 12·5 mg the mean supine blood pressure was 142/94 ± 5·3/3·6 mm Hg, which represented a 13·8% reduction ($p < 0·001$). There was no significant difference in the blood pressure achieved or the absolute or percentage fall in blood pressure with 12·5 mg, 25 mg, or 50 mg of hydrochlorothiazide combined with 400 mg of acebutolol. After four weeks' treatment with acebutolol 200 mg and hydrochlorothiazide 12·5 mg (fig 3) mean average supine blood pressure had fallen to 150/99 ± 4·9/3·4 mm Hg ($p < 0·01$); this represented a 9·4% fall. Although this blood pressure was higher than that after four weeks' treatment with 400 mg acebutolol and 12·5 mg hydrochlorothiazide, it was not significantly different. It was, however, significantly higher than the blood pressure after four weeks' treatment with acebutolol 400 mg and hydrochlorothiazide 25 mg ($p < 0·01$). Mean supine blood pressure measured 24 hours after the final dose of acebutolol 200 mg with

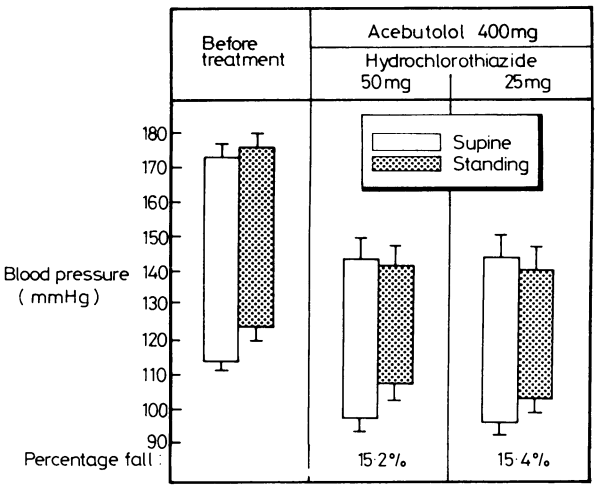

FIG 1—Mean ± SEM blood pressure before and after treatment with acebutolol 400 mg once daily and hydrochlorothiazide either 50 mg or 25 mg once daily for one month in 12 patients.

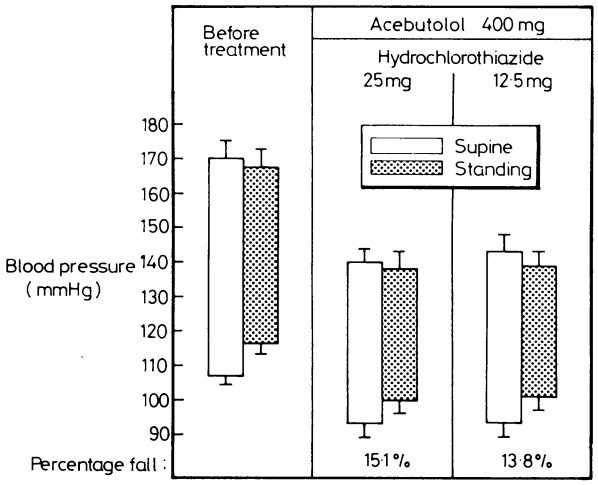

FIG 2—Mean ± SEM blood pressure before and after treatment with acebutolol 400 mg once daily and hydrochlorothiazide either 25 mg or 12·5 mg once daily for one month in 12 patients.

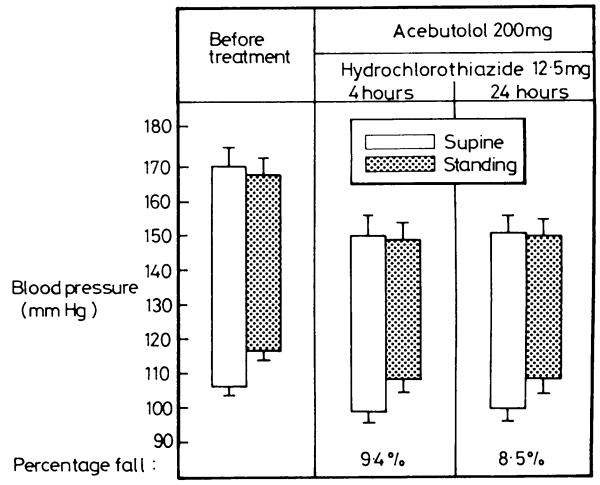

FIG 3—Mean ± SEM blood pressure before and after treatment with acebutolol 200 mg once daily and hydrochlorothiazide 12·5 mg once daily for one month measured four and 24 hours after last dose.

hydrochlorothiazide 12·5 mg was 151/100 ± 5·7/3·2 mm Hg—that is, almost identical with that measured four hours after the final dose.

Standing blood pressure (figs 1, 2, and 3) and blood pressure after exercise (table I) showed changes similar to supine blood pressure in both studies.

Pulse rates supine, standing, and after exercise were significantly reduced four hours after the end of treatment with each combination. Twenty four hours after the end of treatment with acebutolol 200 mg and hydrochlorothiazide 12·5 mg the pulse rate was still reduced compared with pretreatment values but the reduction was significant only on standing (tables I and II).

Blood measurements—Plasma potassium and chloride concentrations fell significantly and plasma bicarbonate concentrations rose in the first study with both 25 mg and 50 mg hydrochlorothiazide combined with 400 mg acebutolol (table II). In the second study there was no significant change in these concentrations with either 25 mg or 12·5 mg hydrochlorothiazide. Plasma uric acid concentration was increased after all drug combinations and was not significantly different between the combinations. Blood urea concentration increased significantly with hydrochlorothiazide 50 mg. In the first study plasma renin activity rose from 0·77 ± 0·15 nmol/l/h (1·0 ± 0·2 ng/ml/h) before treatment to 1·48 ± 0·31 nmol/l/h (1·9 ± 0·4 ng/ml/h) ($p < 0·05$) after four weeks' treatment with hydrochlorothiazide 50 mg and acetbutolol 400 mg (table II). With hydrochlorothiazide 25 mg plasma renin activity did not change and was 0·73 ± 0·15 nmol/l/h (0·95 ± 0·2 ng/ml/h), at the end of treatment. The difference in plasma renin activity after four weeks' treatment with 50 mg or 25 mg of hydrochlorothiazide was significant ($p < 0·003$). In the second study plasma renin activity was 0·53 ± 0·23 nmol/l/h (0·69 ± 0·3 ng/ml/h) before treatment. After four weeks' treatment with 25 mg hydrochlorothiazide and acebutolol 400 mg it was 0·52 ± 0·15 nmol/l/h (0·70 ± 0·2 ng/ml/h), and after four weeks' treatment with acebutolol 400 mg and hydrochlorothiazide 12·5 mg it had fallen to 0·4 ± 0·15 nmol/l/h (0·52 ± 0·2 ng/ml/h).

Weight and side effects—A significant fall in weight occurred with the 50 mg dose of hydrochlorothiazide, but otherwise changes in weight were not significant. No serious side effects were reported in either study. Four patients had slight headaches, but this did not necessitate stopping treatment.

Discussion

This study shows that a once daily combination of a beta-blocker, acebutolol, and a thiazide diuretic, hydrochlorothiazide, is effective in lowering blood pressure in mild to moderate essential hypertension. The fall in blood pressure was identical, however, whether 12·5 mg, 25 mg, or 50 mg hydrochlorothiazide was used in combination with 400 mg acebutolol. This flat dose response to a thiazide diuretic in the presence of a beta-blocker shows that low doses of thiazide diuretics may be used combined with a beta-blocker to treat hypertension in a similar fashion to when the diuretics are used alone.[1 2] Our study does not, however, define the lowest dose of a thiazide diuretic that is effective as we did not use a dose lower than 12·5 mg hydrochlorothiazide. This flat dose response is important because of the increasing adverse metabolic consequences of using unnecessarily high doses of thiazide diuretics.[1] This was seen in our study particularly when 50 mg hydrochlorothiazide was used in combination with the beta-blocker: compared with control values there was a significant increase in blood urea and bicarbonate concentrations and plasma renin activity and a significant fall in plasma potassium and chloride concentrations and weight. The significant fall in plasma potassium concentration occurred even though the beta-blocker is claimed to mitigate the fall in plasma potassium concentration that occurs with diuretics.

The flat dose response of blood pressure to thiazide diuretics alone is at least partly due to the compensatory rise in renin release and angiotensin II concentration caused by the diuretic as the dose is increased.[3] Beta-blockers inhibit sympathetically mediated renin release from the juxta glomerular apparatus and thereby cause a fall in circulating angiotensin II concentrations. This has been claimed to be part of the mechanism whereby beta-blockers alone may lower blood pressure.[5] Suppression of renin release and thereby angiotensin II by beta-blockers in the presence of a diuretic has also been claimed to be part of their additive action. Our study shows that despite the presence of a

TABLE I—*Mean ± SEM blood pressure and pulse rate one minute after treadmill exercise (n=12)*

Treatment: Acebutolol (mg)	Treatment: Hydrochlorothiazide (mg)	Hours after treatment	Blood pressure (mm Hg)	Pulse (beats/min)
			First study	
Before treatment			184/114 ± 5·6/2·6	97 ± 4
400	50	4	143***/100*** ± 6·3/4·1	84*** ± 4
400	25	4	144***/98*** ± 3·7/2·6	83*** ± 3
			Second study	
Before treatment			193/114 ± 7·9/3·0	99 ± 3
400	25	4	151***/96*** ± 6·0/4·0	88** ± 4
400	12·5	4	152***/99* ± 8·0/4·9	82*** ± 3
200	12·5	4	161***/105* ± 7·0/2·9	87* ± 3
		24	171***/105** ± 6·0/3·0	95 ± 4

Significance of difference from pretreatment value: *$p < 0·05$; **$p < 0·01$; ***$p < 0·001$.

TABLE II—*Effect of treatment on plasma biochemistry, weight, and pulse rate (expressed as means ± SEM) (n=12)*

Treatment: Acebutolol (mg)	Treatment: Hydrochlorothiazide (mg)	Hours after treatment	Plasma renin activity (nmol/l/h)	Plasma potassium (mmol/l)	Plasma urea (mmol/l)	Plasma urate (nmol/l)	Plasma chloride (mmol/l)	Plasma bicarbonate (mmol/l)	Weight (kg)	Pulse (beats/min): Supine	Pulse (beats/min): Standing
						First study					
Before treatment			0·77 ± 0·15	3·85 ± 0·1	4·8 ± 0·4	338 ± 31	101 ± 0·8	24 ± 0·4	76·0 ± 4·1	77 ± 4	85 ± 4
400	50	4	1·48* ± 0·31	3·53* ± 0·1	5·5* ± 0·3	424* ± 45	98* ± 0·8	26* ± 0·3	74·3* ± 3·9	67** ± 3	73** ± 3
400	25	4	0·73 ± 0·15	3·67* ± 0·1	5·5 ± 0·4	408** ± 26	99* ± 0·8	25** ± 0·4	74·8 ± 3·7	69** ± 4	75 ± 4
						Second study					
Before treatment			0·53 ± 0·23	3·91 ± 0·1	5·3 ± 0·7	318 ± 21	102 ± 0·9	25 ± 0·3	77·8 ± 3·7	77 ± 3	85 ± 3
400	25	4	0·52 ± 0·15	4·06 ± 0·1	5·4 ± 0·3	380*** ± 24	101 ± 0·8	27 ± 0·4	77·9 ± 3·7	67** ± 3	76* ± 3
400	12·5	4	0·4 ± 0·15	4·03 ± 0·1	5·6 ± 0·3	373** ± 29	102 ± 0·9	26 ± 0·3	77·8 ± 3·9	65** ± 2	73** ± 3
200	12·5	4	0·28 ± 0·15	3·89 ± 0·1	5·5 ± 0·4	372** ± 38	101 ± 0·8	26 ± 0·3	78·1 ± 3·7	68** ± 3	74*** ± 3
		24							78·3 ± 3·7	71 ± 2	79* ± 2

Significance of difference from pretreatment value: *$p < 0·05$; **$p < 0·01$; ***$p < 0·001$.

Conversion: SI to traditional units—Plasma renin activity: 1 nmol/l/h ≈ 1·3 ng/ml/h. Potassium: 1 nmol/l = 1 mEq/l. Urea: 1 mmol/l ≈ 6 mg/100 ml. Urate: 1 nmol/l ≈ 16·8 ng/100 ml. Chloride: 1 mmol/l = 1 mEq/l. Bicarbonate: 1 mmol/l = 1 mEq/l.

beta-blocker a progressive rise in plasma renin activity occurs with increasing doses of a thiazide diuretic, albeit this is a lower rise than would occur if the patients were taking a thiazide diuretic alone. Plasma renin activity was significantly higher after four weeks' treatment with acebutolol 400 mg and hydrochlorothiazide 50 mg than before treatment. With 12·5 mg of hydrochlorothiazide and acebutolol 400 mg plasma renin activity was actually lower than before treatment, though not significantly so. This increased release of renin with increasing doses of diuretic despite the presence of a beta-blocker is probably part of the mechanism explaining the flat dose response to the diuretic. Further work needs to be done, however, using either competitive inhibitors of angiotensin II or converting enzyme inhibitors in conjunction with a beta-blocker and a diuretic, to clarify this point.

The effect of reducing the dose of the beta-blocker from 400 mg to 200 mg was also examined in combination with 12·5 mg hydrochlorothiazide. Acebutolol 200 mg significantly lowered blood pressure by 9·4% while acebutolol 400 mg lowered it by 13·8%. Thus it appears that, when used in combination with hydrochlorothiazide, 400 mg acebutolol is more effective in lowering blood pressure than 200 mg, but further stu 'ies need to be done to clarify the upper and lower limits of the dose response curve for the beta-blocker when used with a diuretic. The effective half life of beta-blockers in lowering blood pressure is longer than might be expected from the clearance of the drugs from the plasma. The duration of action of the lowest dose combination used in this study—acebutolol 200 mg with hydrochlorothiazide 12·5 mg—was therefore examined. The significant reduction in mean blood pressure achieved with this combination at four hours was unchanged at 24 hours. Thus it is reasonable to expect that the combination of 400 mg acebutolol with 12·5 mg hydrochlorothiazide would also be effective for 24 hours after dosing, although this was not examined in this study.

This study did not define the minimum dose of diuretic, and a dose of hydrochlorothiazide less than 12·5 mg might possibly be as effective. In the meantime, our results suggest that many preparations that combine a beta-blocker and a diuretic contain too much thiazide diuretic. This higher dose of diuretic will have adverse metabolic consequences to the patient without further lowering the blood pressure. A low but effective dose of diuretic is less likely to result in adverse effects and should reduce the cost of treatment, conferring obvious advantages in terms of patient acceptability and compliance. Our results also indicate that in patients whose blood pressure is not controlled by the lower dose of diuretic combined with a beta-blocker there is little point in increasing the dose of diuretic. To obtain better control it might be more appropriate to add a third drug such as a vasodilator or change to an angiotensin converting enzyme inhibitor combined with a diuretic, or to a calcium entry antagonist.

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ONE HUNDRED YEARS AGO In their costumes, no less than in their customs and character, a great and general improvement has been seen in nurses, and especially in hospital nurses, during the last five and twenty years. Today the satires of Dickens on the Gamps of his time, terribly true when they were written, are only amusing anachronisms, which the younger generation can scarcely realise as faithful historical portraits. While, however, in personal fitness for her work, in manner, intelligence, kindness, training and skill, the average nurse of a well-conducted hospital now presents a great and in all respects admirable advance upon many of her predecessors of a quarter of a century ago, we still observe that there is room for further improvement in several distinct details of our nurse's attire. The particulars we notice must not be regarded as trivialities which are of no practical moment; we only refer to points which we deem of substantial importance in regard to their effects upon the comfort and progress of the sick persons whom nurses attend. Persons who are ill usually have time to notice, and usually are so hyper-sensitive as to be fretted by a great many comparatively minor details which do not annoy those who are whole, even when they attract their attention. In hospitals a distinct "uniform" is now generally worn by nurses, and this generally consists of a dress of a certain chosen colour and texture, and a white cap or head-dress of some approved pattern. Why should the colour of the nurses' dress usually be black? That lugubrious tint can neither please the senses of the sick nor awaken happy associations in their minds. Dresses of some bright and pretty pattern would be far preferable to the melancholy garments now affected by many hospital nurses, and especially by some who belong to ecclesiastical sisterhoods. Apart from its colour, there is one cardinal quality of a nurse's dress which is not always to be found: the texture of the garments ought to be so soft that the dress adapts itself noiselessly to the movements of its wearer, and does not keep up that monotonous rustling which is so peculiarly irritating to nervous patients. It is obvious that a nurse's tread should be as free from noise as possible; this consummation cannot be attained unless her foot presses a sole which is of even thickness throughout, and unless her whole shoe is so flexible as to be wholly free from the irritating vice of creaking. Heels added to boots or shoes give a stumping noise in walking peculiarly their own. A nurse should wear slippers, without heels, and made of a material so soft as never to give a suspicion of a creak. Whatever her other qualities and characteristics, a sick-nurse may do much to brighten a sick-room and to save her patient from annoyance, and so to add to his comfort and favour his recovery, by scrupulous attention to her own appearance and attire, so that she may be good to look upon, and able to move about her duties without needless noise. (*British Medical Journal*, 1883;ii:737.)

ONE HUNDRED YEARS AGO We are glad to learn that the authorities of board-schools in some large towns are now giving their attention to the physical, as well as the mental, training of the children under their charge. Systematic instruction, by special teachers, in the simpler gymnastic exercises, is being given in some schools twice, or oftener, weekly, being officially recognised as an integral portion of the education to be afforded to boys and girls alike; and proficiency in physical performances is being stimulated and rewarded by occasional public displays and by suitable prizes and distinctions. This is as it should be, and we hope the good practice to which we refer may soon become general throughout the schools of the country. Those who have the care of young persons in schools may do much in aiding the physical development of their pupils; and, as a consequence, in making their lives longer and happier, by the judicious use of the gymnasium. (*British Medical Journal* 1883;i:468.)