Captopril in essential hypertension; contrasting effects of adding hydrochlorothiazide or propranolol

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Abstract

Twenty-four patients with moderate to severe hypertension were treated for four weeks with captopril, an oral inhibitor of angiotensin-converting enzyme. The fall in blood pressure with captopril alone correlated with pretreatment plasma renin activity. The effect of adding either hydrochlorothiazide or propranolol to the captopril treatment was then studied. The addition of hydrochlorothiazide to captopril produced a dose-dependent fall in blood pressure. At the higher dose of the diuretic this fall in blood pressure correlated with weight loss, suggesting that when the diuretic-induced compensatory rise in angiotensin II is prevented by captopril the fall in blood pressure becomes dependent on loss of sodium and water. In contrast, the addition of propranolol to captopril produced no further fall in blood pressure, suggesting that inhibition of angiotensin-converting enzyme prevents the blood pressure lowering effect of propranolol. This may have implications for the mechanism whereby beta-blockers alone lower blood pressure.

These contrasting effects of hydrochlorothiazide and propranolol in the presence of captopril indicate that in patients whose hypertension is not controlled by captopril alone the addition of increasing doses of diuretic is likely to control the blood pressure. The addition of a beta-blocker, however, is less likely to be effective.

Introduction

Inhibition of the angiotensin-converting enzyme is an effective way of lowering blood pressure,1-7 but acceptable blood pressure control is not always obtained by inhibiting converting enzyme alone, especially in patients with severe hypertension and low renin.4 5 On theoretical grounds the addition of a diuretic to captopril should be particularly effective, as captopril will block the compensatory rise in angiotensin II caused by the diuretic.6-9 The addition of a beta-blocker to captopril may not, however, be as effective as the combination of captopril and a diuretic.

In two carefully controlled clinical trials we therefore examined the effects of adding either a thiazide diuretic (hydrochlorothiazide) or a beta-blocker (propranolol) in patients with moderate to severe essential hypertension already receiving captopril. These trials were done before it was known that captopril may very rarely cause leucopenia. Captopril is now recommended by the manufacturers only in patients who are resistant to conventional drug treatment or who have severe side effects with conventional treatment.

Patients and methods

Patients with uncomplicated moderate to severe essential hypertension were studied. Patients were excluded if there was evidence of renal failure, ischaemic heart disease, or cerebrovascular disease or if they were taking oral contraceptives or any other drug. Informed consent was obtained from each patient. Patients had either not received treatment for their blood pressure or, if they had, treatment had been stopped at least two weeks before entry to the study.

There were two separate studies. In the first captopril and hydrochlorothiazide were given to 16 patients (9 men, 7 women; 12 blacks and 4 whites; mean age 52 years (range 42-61)) with moderate to severe hypertension (mean supine diastolic blood pressure 121 mm Hg
(range 104-140)). In the second study captopril and propranolol were given to eight patients (5 men, 3 women; 1 black, 7 whites; mean age 53 years (range 43-65)) with moderate hypertension (mean supine diastolic blood pressure 113 mm Hg range 105-121).

In the first study captopril was given thrice daily, 25 mg for one week, 50 mg for the second week, 100 mg for the third week, and 150 mg for the fourth week. Hydrochlorothiazide 25 mg twice daily was then added to captopril for two to four weeks. In 11 patients in whom the diastolic pressure was still greater than 95 mm Hg hydrochlorothiazide 50 mg twice daily was given with captopril for a further four to six weeks.

In the second study the eight patients received four weeks of matching placebo before starting captopril. The treatment period with captopril alone was identical to that in the first study, increasing weekly from 25 mg three times a day in the first week to 150 mg three times a day in the fourth. Propranolol 20 mg three times a day was then added for a fifth week. Two patients experienced adverse effects at this stage and treatment was stopped. In the remaining six patients the dose of propranolol was increased to 40 mg three times a day in the sixth week. One other patient developed a side effect and was withdrawn, allowing five patients to continue to the seventh week with propranolol 80 mg three times a day in addition to captopril.

All patients were seen weekly in the blood pressure clinic at the same time of day by the same nurse. Patients were told to take their tablets two to three hours before visits so that measurements were done within two to four hours after the last dose of captopril. All blood pressures were measured with a semi-automatic ultrasound sphygmomanometers (Arteriosonde 1217) with chart recorders. The measurement was therefore free of observer bias. We used the mean value of five readings taken at 1- to 2-minute intervals with the patient supine and standing. Pulse rate was measured on a Cambridge 3048 pulse monitor. Weight was measured at each visit.

Blood samples for estimating plasma renin activity and plasma aldosterone, urea, electrolyte, and creatinine concentrations were taken before active treatment and every one or two weeks thereafter. Blood was taken without stasis after the patient had been sitting upright for five minutes. Plasma renin activity and aldosterone were measured by radioimmunoassay. The normal ranges for plasma renin activity and plasma aldosterone with a sodium intake of 100-200 mmol/day are 0.5-2.5 ng/ml/h and 100-600 pmol/l respectively. All patients ate their normal diet, and their 24-hour urinary sodium excretion before treatment ranged from 104-190 mmol/(mEq).

Mean arterial pressures were calculated as 1/3 pulse pressure + diastolic pressure. Results were reported as means ± SEM and were analysed by the paired Student's t test and least squares linear regression.

Results

captopril and Hydrochlorothiazide

By the fourth week, when patients were taking only captopril 150 mg three times a day, mean blood pressure had fallen by 9% (p < 0.05). The addition of hydrochlorothiazide 25 mg twice a day produced a further fall (p < 0.001 compared to the last week of captopril alone), resulting in an overall reduction in mean supine blood pressure of 19% (fig 1). When hydrochlorothiazide was increased to 50 mg twice a day there was a further fall in blood pressure (p < 0.001). The final supine blood pressure was 138/96 ± 3/3 mm Hg, which represented an overall reduction in blood pressure of 25%. Throughout the trial changes in standing blood pressures were similar to those of supine pressures. There was no evidence of postural hypotension.

Mean plasma aldosterone concentrations fell, though not significantly, with captopril alone and did not rise after the addition of hydrochlorothiazide in spite of the rise in plasma renin activity. Mean body weight fell from 76·1 to 74·9 kg (p < 0.001) in the 16 patients when hydrochlorothiazide 25 mg twice a day was added to captopril, and from 80·8 to 79·4 kg (p < 0.001) in the 11 patients taking 50 mg hydrochlorothiazide twice a day. The percentage fall in mean blood pressure after hydrochlorothiazide 50 mg twice a day was added was significantly related to weight loss in these 11 patients (r = 0.64; p < 0.05). Plasma potassium concentrations fell from 4·1 to 3·8 mmol/(mEq/l) after patients received 25 mg hydrochlorothiazide twice a day in addition to captopril and from 4·1 to 3·5 mmol/l (p < 0.005) in the 11 patients after 50 mg hydrochlorothiazide twice a day. Among these 11 patients the lowest final plasma potassium concentration was 2·8 mmol/l, and five patients had a plasma potassium value below 3·5 mmol/l on the combination of captopril and 50 mg hydrochlorothiazide twice a day (table I).

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| TABLE I—Effect of increasing doses of captopril and of adding hydrochlorothiazide to captopril 150 mg three times a day in 16 patients with moderate to severe hypertension. Values are means ± SEM. |
|---------------------------------|------------------|------------------|------------------|
|                                 | Baseline         | Captopril (three times a day): | Hydrochlorothiazide (twice a day): |
|                                 | 25 mg            | 50 mg            | 100 mg                                      | 150 mg                                      | 25 mg (n = 16) | 50 mg (n = 11) |
| Mean supine blood pressure (mm Hg) | 142 ± 3          | 136 ± 3          | 142 ± 2                                    | 132 ± 4                                    | 129 ± 4       | 114 ± 3       |
| Supine pulse rate (min)         | 81 ± 3           | 78 ± 3           | 81 ± 3                                     | 81 ± 3                                     | 81 ± 2        | 79 ± 2        |
| Weight loss (kg)                | 0.2 ± 0.2        | 0.1 ± 0.2        | 0.4 ± 0.2                                  | 0.3 ± 0.3                                  | 1.4 ± 0.3     | 1.7 ± 0.5     |
| Plasma aldosterone (pmol/l)     | 261 ± 38         | 246 ± 33         | 212 ± 35                                   | 193 ± 29                                   | 190 ± 26      | 229 ± 39      |
| Plasma potassium (mmol/l)       | 3.9 ± 0.1        | 4.0 ± 0.1        | 4.1 ± 1                                     | 4.1 ± 1                                     | 3.8 ± 0.1     | 3.3 ± 0.1     |

*p < 0.05 compared to control.  
**p < 0.001 compared to captopril 150 mg three times a day.

Conversion: SI to traditional units—Aldosterone: 1 pmol/l = 36 pg/100 ml. Potassium: 1 mmol/l = 1 mEq/l.
Blood pressure did not change after four weeks of taking placebo. Mean blood pressure fell significantly after the first week of captopril 25 mg three times a day. By the fourth week, when patients were taking 150 mg captopril three times a day, mean supine blood pressure had fallen by 21% (p < 0.001). When propranolol 20 mg three times a day was added diastolic and mean supine blood pressure rose significantly (p < 0.005) (fig 2). With 40 mg propranolol three times a day a blood pressure remained significantly raised (156/99 ± 7/4 mm Hg; p < 0.025) and did not change in the five patients who received 80 mg three times a day (155/92 ± 7/3 mm Hg).

Discussion

The results of this study confirm that captopril alone lowers blood pressure in patients with moderate to severe essential hypertension. As others have found, the fall in blood pressure with captopril alone was related to the activity of the renin-angiotensin system before treatment. This could explain the smaller fall in blood pressure with captopril alone in the patients who went on to receive hydrochlorothiazide, as they had more severe hypertension and a lower mean pretreatment plasma renin activity.

The addition of hydrochlorothiazide to captopril produced a pronounced further fall in blood pressure, and this fall was related to the dose of diuretic, in that there was a further fall in blood pressure in the 11 patients whose dose of hydrochlorothiazide was increased to 50 mg twice a day. Several studies have suggested that the effectiveness of diuretics alone in reducing blood pressure is limited by the compensatory rise that occurs in plasma renin activity and thereby in plasma angiotensin II and aldosterone values. By inhibiting angiotensin-converting enzyme captopril will block the rise in plasma angiotensin II and aldosterone that normally occurs with the addition of hydrochlorothiazide. Blood pressure should be decreased on sodium and water balance, analogous to the position in anephric subjects on dialysis. A fall in blood pressure with the addition of a diuretic to captopril should therefore be related to the loss of sodium and water caused by the diuretic, which would be reflected in the weight loss. The fact that plasma aldosterone did not rise with the addition of hydrochlorothiazide to captopril and the significant relationship between weight loss and the fall in blood pressure on 50 mg of hydrochlorothiazide twice a day supports the above concept.

Plasma renin activity before active treatment was within the normal range in seven patients and low in one. Plasma renin activity rose by 0.89 ng/ml/h (p < 0.001) after one week of captopril and remained at this level with increasing doses. When propranolol was added plasma renin activity fell in all patients (p < 0.005), and the resulting mean level was below the pretreatment control value (fig 2). Changes in mean blood pressure, pulse rate, weight, and plasma aldosterone and potassium concentrations with captopril alone and after the addition of propranolol are shown in table II.

When all the patients in both groups were considered together the percentage fall in mean blood pressure by the fourth week of treatment with captopril alone (150 mg three times a day) was significantly related to log initial plasma renin activity (r = -0.48, p < 0.05, n = 24).

SIDE EFFECTS

Captopril was well tolerated. Three patients, however, lost the sensation of taste after five weeks of captopril and one week of propranolol 20 mg three times a day. Two were withdrawn at the end of the week on this combination and the third at the end of the week of captopril and propranolol 40 mg three times a day. Taste sensation returned rapidly to all three when they stopped captopril. No patient developed proteinuria, rash, or leucopenia.

It has been claimed that inhibition by captopril of the diuretic-induced rise in angiotensin II and aldosterone prevents the fall in plasma potassium concentration seen with diuretics alone. In our study, however, the addition of 50 mg hydrochlorothiazide twice a day to captopril resulted in hypokalaemia in almost half the patients.

The effectiveness of the combination of captopril and a thiazide diuretic may be seen both by the percentage fall in blood pressure that occurred (25%) and by the fact that of our patients with a mean pretreatment diastolic pressure of 122 mm Hg only two had a diastolic pressure of over 100 mm Hg at the end of the trial. Our experience in 29 patients with treatment-resistant hypertension given captopril and a diuretic alone for more than six months supports other evidence that the combination of captopril and a diuretic alone is particularly effective in the long-term control of treatment-resistant hypertension. Many of the 29 patients with treatment-resistant hypertension were considered to have resistant hypertension because they had not responded, or only partially, to previous therapy and had been referred to a hypertension clinic for management of their problem.
hypertension did, however, need the addition of loop diuretics such as frusemide to induce the required loss of sodium and water.

In contrast to the effect of hydrochlorothiazide, the addition of propranolol to captopril produced a significant rise in blood pressure. All blood pressure measurements were, however, taken two to four hours after dosing, when captopril was likely to be exerting its maximum effect on blood pressure. In a similar study Lederle et al.11 showed no significant change in blood pressure when propranolol was added to captopril. This may have some implications for the mechanism whereby beta-blockers alone lower blood pressure. It is of interest that a rise in blood pressure occurred in both treatments alone has been seen in some patients with low-renin hypertension.15 Nevertheless, the addition of propranolol to captopril did cause a significant fall in pulse rate and reduced the captopril-induced high plasma renin activity to below pretreatment values. This latter observation shows that propranolol inhibits the increased renin release caused by captopril. Possibly propranolol, though inhibiting renin release, may prolong the length of action of captopril, so that if blood pressure was measured at a longer interval after dosing an apparent additive action of the two drugs might be seen.

In this short-term trial captopril was well tolerated, except for loss of taste in three patients, which recovered fully when they stopped taking captopril. The study does not indicate the minimum effective dose of captopril when combined with a diuretic. However, in a previous experience in patients with treatment-resistant hypertension given captopril suggests that much lower doses of captopril—that is, 12.5 to 25 mg three times a day—are almost as effective as the larger doses used in this trial when combined with a diuretic. These lower doses might reduce the incidence of problems that have been seen with captopril, such as rash, loss of taste,16 membranous glomerulonephritis,17 and leucopenia in patients with renal failure.18 Inhibition of angiotensin-converting enzyme combined with a diuretic is likely to play an increasing part in the management of treatment-resistant hypertension and, if these drugs are shown to be well tolerated in the long term, an increasing part in the management of essential hypertension.

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References


ONE HUNDRED YEARS AGO

The profession will be grateful to the National Health Society for endeavouring to demonstrate the evils of tight lacing to popular audiences. I fear, however, that Mr Treves, in his recent lecture at Kensington, treated the subject a little too confidently from a sanitary and a little too cavalierly from an aesthetical, point of view. I should be very sorry if anything I said could be looked on as an encouragement to tight lacing by ladies; but still I think we should take them into our councils, and discuss the subject in all its bearings with moderation. I think that Mr Treves fell into an important error when he assumed that the primary use of dressing was to cover the body and maintain an equable temperature; and again, when he asserted that a small waist in a draped figure is ugly, and offends our sense of the beautiful in the human form. Now, all anthropologists agree that the primary object of dress was decoration, and this is the use of tight lacing, on the one hand, and of curving the body, on the other, a part of the third of the grand proportions. A custom which is so general must have some raison d'être, although women cannot explain it. Some women think that men admire small waists; and, until the question is decided by a vote by ballot, they will not believe otherwise. In truth, small waists are a draped figure of the human form which is at the bottom of our sense of the beautiful, not only in the human form, but in all other objects. Professor Zeising, to whom we owe the discovery of this law, states it thus: “If the divisions of a whole (made up of unequal parts) appear proportional, the smaller part will bear the same relation to the larger that the larger does to the whole.” Now the waist forms the division of the body which gives these proportions. Thus, if we take a well proportioned figure, and represent its total height by 1,000, we shall find the portion below the waist is represented by 618, and the portion above it by 382 parts; and 382 is to 618 what 618 is to 1,000. Zeising’s law applies equally well to the hand, the head, the arm, and the leg; and, indeed, to all animate and inanimate objects which appear proportional to us. But in some nude figures, the proportional division is not at the waist, but at the knees. In the Venus de Milo, where the face is across the body, this is the case; hence the charm of young girls with short skirts and no waists (and perhaps of men in frock coats). The shorter the skirts in the children, the better the proportion appears; but as they grow up, and their skirts are lengthened, a new division line becomes necessary, and the waist is constructed accordingly. The dress reformers should, therefore, bear in mind that dressing is the instinct of decorating the body, and that a small waist is the result of a law of nature; but within these limits there is ample room for their efforts for improvement; many dresses are fantastically bad in taste, and most waists are constructed too much even from an aesthetical point of view. (British Medical Journal, 1882.)