CAPTOPRIL AND ATENOLOL COMBINED WITH HYDROCHLOROTHIAZIDE IN ESSENTIAL HYPERTENSION

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- 1 Fifty-seven patients with mild or moderate essential hypertension, mean age 50 (range 31–69) were randomised to treatment with either captopril or atenolol. Twenty-six patients in each group completed the study.
- 2 Captopril (25–50 mg three times daily) and atenolol (50–100 mg once daily) caused a highly significant fall in blood pressure both supine and standing.
- 3 When hydrochlorothiazide (25–50 mg once daily) was added a further fall in blood pressure was observed in both groups.
- 4 Captopril as single drug caused no significant change in heart rate, while atenolol significantly reduced heart rate both supine and standing.
- 5 Two patients were excluded from the captopril group, one because of a reversible loss of taste and the other because of dizziness. Three patients were excluded from the atenolol group, two because of bradyarrhythmias and one because of inadequate blood pressure response.
- 6 Both captopril and atenolol were found to be effective antihypertensive agents, suitable for the treatment of essential hypertension.

Introduction

Captopril is an orally active inhibitor of the angiotensin I-angiotensin II-converting enzyme (Ondetti *et al.*, 1977). Inhibition of this enzyme also prevents the kinase II-mediated degradation of bradykinin (Fox *et al.*, 1961). The renin-angiotensin-aldosterone system is of pathogenetic importance in renovascular hypertension, while no such connection has been found in essential hypertension (Beevers *et al.*, 1977). Captopril can reduce blood pressure both in renovascular and essential hypertension (Atkinson & Robertson 1979; Gavras *et al.*, 1978; Bravo & Tarazi, 1979; Atlas *et al.*, 1979). Opinions differ whether its blood-pressure lowering effect in essential hypertension is correlated with plasma renin activity (Laragh, 1978; Case *et al.*, 1978; Karlberg *et al.*, 1981; Bravo & Tarazi, 1979; Gavras *et al.*, 1978; Johnston *et al.*, 1979). That captopril can reduce blood pressure independently of circulating renin and angiotensin II concentrations is shown by its antihypertensive effect in anephric patients (Vaughan *et al.*, 1979; De Bruyn *et al.*, 1980).

Atenolol is a β_1 -selective adrenoceptor-blocking agent. Its usefulness in antihypertensive treatment is

well documented (Hansson *et al.*, 1975; Wilcox, 1978).

The purpose of this study was to compare the antihypertensive effect of captopril and atenolol as single drugs and in combination with hydrochlorothiazide in patients with essential hypertension.

Methods

Fifty-seven patients with mild-to-moderate essential hypertension (36 men, 21 women) were recruited for the study. Their mean age was 50 (range 31–69). Secondary hypertension was excluded by routine investigations. Twenty-three patients had newly detected hypertension and had not been treated, while 34 were receiving antihypertensive treatment. All previous antihypertensive treatment was withdrawn at least 2 weeks before the study started and all patients were put on placebo for 2 weeks.

A supine diastolic blood pressure of 100–125 mm Hg at the end of the placebo period was the criterion for inclusion in the study. The patients were then

randomised to treatment with either captopril ($n = 28$) or atenolol ($n = 29$). The therapeutic goal was to reach normotension, defined as supine diastolic blood pressure of 90 mm Hg or less.

The total duration of the study was 14 weeks and the period of active drug treatment was 12 weeks. The patients were seen every second week and blood pressure and side effects were assessed on each occasion. If supine diastolic blood pressure was 95 mm Hg or more the dosage of captopril and atenolol was increased in a stepwise design (Figure 1). The initial dose of captopril was 25 mg three times daily. It was doubled after two weeks if normotension was not achieved. After further two and four weeks hydrochlorothiazide was added (25 mg and 50 mg once daily) if needed to reach normotension. The final dose step was to increase captopril to 100 mg three times daily, while hydrochlorothiazide was kept at 50 mg once daily (Figure 1).

The corresponding dose levels for atenolol were 50 mg and 100 mg once daily. Hydrochlorothiazide 25 mg or 50 mg once daily was added if necessary to obtain normotension. The final dose step was to increase atenolol to 200 mg once daily, while the dosage of hydrochlorothiazide was kept at 50 mg once daily (Figure 1).

If at any visit the patient was normotensive there was no change in dose on that occasion. If, however, the supine diastolic blood pressure was 95 mm Hg or more at the next visit, the dose was further increased according to the scheme in Figure 1.

All patients were treated as outpatients and the blood pressure was measured with a mercury sphygmomanometer with a 12-cm wide cuff containing a 30-cm rubber balloon. The mean of three measurements was used for blood pressure calculations. Supine blood pressure was measured after five minutes of rest and standing blood pressure after one–two minutes. All measurements were made under strictly standardised conditions by specially trained nurses. The disappearance (phase 5) of the Korotkoff sounds was taken as the diastolic blood pressure.

Student's t test for paired and non-paired data was used for statistical evaluation.

The study was approved by the ethical committees at the universities of Göteborg and Linköping.

Results

Captopril (25–50 mg three times daily) caused a highly significant decrease in both supine (13/10 mm Hg) and standing (14/10 mm Hg) blood pressure (Table 1). Captopril alone produced normotension in 37% of the patients after four weeks of treatment. Heart rate was not significantly changed by captopril treatment (Table 1).

Atenolol (50–100 mg once daily) also caused a highly significant reduction in both supine (17/13 mm Hg) and standing (15/13 mm Hg) blood pressure (Table 2). After four weeks of treatment 32% of the patients were normotensive in the atenolol group. Heart rate was significantly reduced both supine and standing by atenolol (Table 2).

Twenty patients in the captopril group and 18 patients in the atenolol group required the addition of hydrochlorothiazide (Table 1).

In the captopril group 73% became normotensive, while the corresponding figure in the atenolol/hydrochlorothiazide group was 69%. The total reduction in supine and standing blood pressure in the captopril group after 12 weeks of active treatment was 32/21 mm Hg and 35/21 mm Hg respectively (Table 1). The corresponding reduction in blood pressure in the atenolol group was 32/18 mm Hg and 32/21 mm Hg (Table 2).

There was a significant increase in standing heart rate after the addition of hydrochlorothiazide in the captopril group, while heart rate was significantly reduced both supine and standing in the atenolol/hydrochlorothiazide group. The difference in heart rate between the two groups was statistically significant.

There were 26 patients in each group who com-

Figure 1 Design of study

C = captopril; A = atenolol; H = hydrochlorothiazide.

Table 1 Supine and standing blood pressure and heart rate in patients receiving captopril and details of captopril and added hydrochlorothiazide dosage.

	<i>End placebo</i>	<i>Week 6</i>	<i>Week 14</i>
Supine blood pressure (mm Hg)	164/108	*** ** 151/98	*** ** 132/87
Supine heart rate (beats/min)	71	73	76
Standing blood pressure (mm Hg)	165/115	** ** 151/105	*** ** 130/94
Standing heart rate (beats/min)	79	82	** 87
Dosage (mg)	Placebo (28)	75 (12) 150 (15)	75 (4) 150 (2) 75+H25 (1) 150+H25 (8) 150+H50 (6) 300+H50 (5)

H = Hydrochlorothiazide

** $p < 0.01$; *** $p < 0.001$.**Table 2** Supine and standing blood pressure and heart rate in patients receiving atenolol and details of atenolol and added hydrochlorothiazide dosage.

	<i>End placebo</i>	<i>Week 6</i>	<i>Week 14</i>
Supine blood pressure (mm Hg)	170/109	*** ** 153/96	*** ** 138/91
Supine heart rate (beats/min)	73	*** 55	*** 56
Standing blood pressure (mm Hg)	166/115	*** ** 151/102	*** ** 134/94
Standing heart rate (beats/min)	78	*** 60	*** 61
Dosage (mg)	Placebo (29)	50 (7) 100 (21)	50 (4) 100 (4) 100+H25 (4) 100+H50 (6) 200+H50 (8)

H = Hydrochlorothiazide

*** $p < 0.001$.

pleted the study. In the captopril group one patient dropped out because of loss of taste and one because of dizziness. The ability to taste returned one month after drug withdrawal. Three patients were excluded in the atenolol group, two because of bradyarrhythmias (sick sinus syndrome and sinus bradycardia) and one due to poor blood pressure response.

Discussion

Captopril and atenolol, both as single drugs and in combination with hydrochlorothiazide, caused a significant reduction in both supine and standing blood pressure in patients with mild to moderate essential hypertension. This confirms earlier results

where captopril has reduced blood pressure in patients with essential hypertension (De Bruyn *et al.*, 1980; Karlberg *et al.*, 1981). In some studies there has been a positive correlation between blood pressure reduction with captopril and plasma renin activity (Fagard *et al.*, 1979; Karlberg *et al.*, 1981). In other studies no such connections have been found (Bravo & Tarazi, 1979; Gavras *et al.*, 1978; Johnston *et al.*, 1979).

The acute effects of captopril are probably more closely related to renin concentrations, whereas the long-term effects of the drug appear to be unrelated to renin. This is shown by the drug's good antihypertensive effect in anephric patients (Vaughan *et al.*, 1979; De Bruyn *et al.*, 1980). Inhibition of converting enzyme also prevents the kinase II-mediated degradation of bradykinin (Fox *et al.*, 1961), which is a potent vasodilator. Furthermore, there are reports of a renin-angiotensin system in the vascular wall. When this system is activated there is an increase in vascular tone and resistance (Haber, 1980; Caldwell *et al.*, 1976). There is also some evidence of a renin-angiotensin system in the central nervous system, although this is still debated. There are reports that stimulation of this renin-angiotensin system could cause an increase in blood pressure probably because of interference with the sympathetic nervous system (Schölkens *et al.*, 1980; Ganten *et al.*, 1978). Thus, blockade of the angiotensin I-angiotensin II-converting enzyme with captopril could increase bradykinin, decrease vascular wall angiotensin II, and a decrease in sympathetic tone

which would cause vasodilatation and a decrease in peripheral resistance. Captopril also impairs vascular smooth muscle contractions mediated by post-synaptic α_2 -adrenoceptors (De Jonge *et al.*, 1981). Thus, there are several possible mechanisms by which captopril can reduce blood pressure in essential hypertension. The relative importance of the different renin-angiotensin systems and of bradykinin in this respect remains to be elucidated.

The mode of action of atenolol is also not fully understood. As with other β -adrenoceptor blocking drugs without intrinsic sympathomimetic activity, it appears as if cardiac effects—for example, a reduction in cardiac output—are the most important (Hansson, 1973; Svensson *et al.*, 1981).

From a practical point of view both captopril and atenolol are effective and safe antihypertensive agents that can be used for treating essential hypertension. Both are potentiated by combined use with hydrochlorothiazide. In this study hydrochlorothiazide potentiated the antihypertensive effects of captopril and atenolol by about the same extent, which disagrees with one of our previous observations, in which systolic blood pressure was more effectively reduced when a thiazide was added to captopril than to atenolol (Andrén *et al.*, 1982). Since the number of patients is larger in this series it seems likely that hydrochlorothiazide potentiates captopril and atenolol to the same extent. Nevertheless, conceivably subgroups of patients may respond more to one of these drug combinations than to the other.

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