CLINICAL RESEARCH

Captopril in renovascular hypertension: long-term use in predicting surgical outcome

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Abstract

The angiotensin converting-enzyme inhibitor captopril was used as long-term preoperative treatment in a series of hypertensive patients with unilateral renal arterial disease. There were immediate and sustained falls in plasma angiotensin II and aldosterone concentrations, with converse increases in circulating renin and angiotensin I. In patients with sodium and potassium deficiency and secondary aldosterone excess before treatment captopril corrected the sodium and potassium deficits; in these cases the initial hypotensive response was profound but the later effect was less pronounced. When sodium and potassium state was initially normal it remained unchanged during captopril treatment, while the full hypotensive effect took up to three weeks to be attained. The immediate, but not long-term, falls in arterial pressure with captopril were proportional to the immediate decrements of plasma angiotensin II. Nevertheless, while the immediate blood-pressure reduction with captopril variously overestimated and underestimated the eventual surgical response, the absolute blood-pressure values during long-term captopril related well with those after operation.

Pretreatment plasma renin and angiotensin II concentrations, while closely predicting the immediate captopril response, are fallible guides to surgical prognosis. In contrast, long-term treatment with converting-enzyme inhibitors may provide an accurate indication of surgical outcome.

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Introduction

The role of the renin-angiotensin system in the pathogenesis of renovascular hypertension remains imperfectly defined.[1-3] The evolution of renovascular hypertension can usefully be considered in three phases.[4] In phase 1 the rise in blood pressure is explicable by the direct vasoconstrictor action of raised plasma concentrations of renin and hence angiotensin II.[1] In phase 2 plasma renin and angiotensin II concentrations are lower relative to the blood-pressure values than in phase 1, and this has cast doubt on the pathogenic significance of the renin-angiotensin system in phase 2.[2-4] Angiotensin II, however, has a slow pressor component[3 5 6] in addition to its immediate vasoconstrictor effect, and this could well be important pathogenically in phase 2. Moreover, in phase 2, as in phase 1, relief of renal artery stenosis or excision of the affected kidney may still alleviate the hypertension.[4] In a later, third phase surgical intervention is not effective, and it is therefore important to distinguish phases 2 and 3. The renin-angiotensin system is unlikely to be implicated pathogenically during phase 3; hypertension-induced changes in the contralateral kidney or structural alterations in resistance vessels, or both, have severally been invoked.

Despite these uncertainties about the renin-angiotensin system in the pathogenesis of renovascular hypertension, many workers have employed various inhibitors and antagonists of the system, administered short term, both diagnostically and as a guide to surgical prognosis.[7-11] Furthermore, pretreatment with natriuretic agents, particularly frusemide, has been widely used, ostensibly to unmask the "renin dependency" of hypertension. Sodium depletion, however, consistently raises plasma angiotensin II concentrations and increases dependence on the renin-angiotensin system for the maintenance of arterial pressure both in normal subjects and in hypertension of varied cause. An alarming fall in blood pressure has been observed in essential hypertension on giving captopril after frusemide.[12] Such an approach therefore seems of dubious value in renovascular hypertension.[11 13 14] Not surprisingly, both false-positive and

false-negative results have not been unusual with these various manoeuvres.[9 11 13] We have reviewed diagnostic and prognostic problems in renal hypertension.[14]

The development of orally active inhibitors of angiotensin I converting enzyme has permitted long-term suppression of angiotensin II formation in man.[13 15 16] In the following study we used the converting-enzyme inhibitor captopril in a series of hypertensive patients with a unilateral renal artery lesion. We assessed both immediate and sustained alterations in the components of the renin-angiotensin system in relation to falls in arterial pressure and changes in body sodium and potassium composition. We also compared the results of such preoperative drug treatment with the outcome after surgery.

Patients and methods

Fifteen hypertensive patients (see table) were diagnosed as having unilateral renal arterial stenosis or occlusion by renal arteriography,[14] isotope renography (except case 1),[17] renal vein renin estimations (range of ratios 1·12-7·20:1),[18] and bilateral ureteric catheterisation (except case 15).[14] All assessments in the ward were with the patients taking diets of known sodium and potassium content, fixed within the ranges sodium 113-155 mmol (mEq) and potassium 49-82 mmol (mEq)/24 hours, and the same at each evaluation in each patient. Treatment was stopped at least two weeks before the initial study, except in four patients (cases 1, 7, 9, and 14), in whom bethanidine only was continued until 12 hours before the introduction of captopril.

After fasting overnight, blood samples were drawn from a peripheral vein at 0930 and 1000, immediately before the initial dose of captopril, and two and six hours later, the patients remaining fasting until after the two-hour sample and recumbent until after the six-hour sample. The initial dose was 6·25 mg in cases 6, 7, and 9 and 25 mg in the rest. In 13 patients the dose was increased to 150 mg thrice daily over the next four days; this full dose was attained at nine days in one instance[20] and 50 mg thrice daily at seven days in another.[19]

Six days after starting captopril and while still in hospital the patients were again assessed. Thirteen of them were subsequently followed up in the outpatient clinic for between five and six weeks, taking captopril alone 150 mg thrice daily, and then readmitted and evaluated as before. The values given for renin, angiotensins I and II, and aldosterone at six days and for the fifth and sixth weeks of treatment are the means of the results in samples taken at 1000, 1200, and 1600, respectively, 12, two, and six hours after a 150 mg dose of captopril.

In case 1 unilateral nephrectomy was performed on the eighth day after starting captopril.[19] In case 15 severe hypertension was not controlled with captopril alone, and frusemide was therefore added on the 14th day. In these two cases the last available readings during treatment with captopril alone were considered in evaluating the long-term results.

Ten of the patients came to operation (table), captopril alone being continued up to the day of operation and then stopped. Nine of these patients were later reassessed in the ward, while taking no treatment, at least three months after operation. In the remaining surgically treated patient (case 15) persistent severe hypertension necessitated the reintroduction of antihypertensive drugs only three weeks after operation; the last untreated values postoperatively were therefore considered in this man. In all the postoperative assessments blood samples were obtained in the ward at 0930 after overnight recumbency and fasting.

Plasma active renin[18] (normal range 10-50 mU/l), angiotensin II[21] (5-35 pmol/l; 5-35 pg/ml) and aldosterone[22] (< 500 pmol/l; < 18 ng/100 ml), and blood angiotensin I[23] (10-90 pmol/l; 13-17 pg/ml) concentrations were measured, angiotensin II values during captopril treatment being corrected[24] for cross-reaction with angiotensin I in the plasma extract. Total exchangeable sodium was measured by isotope dilution,[25] and total body potassium using endogenous ^{40}K and external counting[26]; results are expressed in absolute terms in figs 2 and 3.

Apart from the presenting reading, inpatient and outpatient blood pressures were taken after both 10 minutes' lying and two minutes' standing. Phase V was used as the diastolic pressure. Apart from the immediate response to captopril, inpatient values are the means of all readings at 1000, 1200, and 1600 hours. "Mean" blood pressure was taken as diastolic plus one-third pulse pressure. The percentage fall in mean pressure after operation was correlated with the pretreatment plasma renin and angiotensin II concentrations and serum creatinine concentration, as well as with the renal vein renin ratio, to assess the predictive value of these tests. All statistical calculations were with non-parametric methods.

Results

Two hours after the first dose of captopril the plasma angiotensin II concentration had fallen significantly, and this fall was maintained during prolonged treatment (fig 1). Despite the increasing captopril dosage, the absolute values for angiotensin II at two hours, six days, and five to six weeks of treatment were closely similar in individual patients. Concomitantly with the fall in angiotensin II, there were immediate and sustained increases in blood angiotensin I and plasma active renin concentrations (fig 1).

The fall in plasma aldosterone concentration (fig 1) was significantly related to the reduction in plasma angiotensin II at two hours ($r_s = 0·45$; $p < 0·05$) and at five to six weeks ($r_s = 0·73$; $p < 0·01$).

The decrements in systolic and diastolic pressures at two hours were in proportion to the falls in plasma angiotensin II (respectively, $r_s = 0·55$, $p < 0·05$; and $r_s = 0·66$, $p < 0·01$). Though the average reductions in systolic and diastolic pressures in the series remained similar to those at two hours both at six days and at five to six weeks of treatment, there were striking variations in the pattern of individual response (table).

Two patients (cases 1 and 11)—one of whom (case 1) was the subject of a previous report[19]—were, before treatment, examples of the so-called hyponatraemic hypertensive syndrome,[27] being depleted of sodium and with low plasma concentrations of sodium and potassium, pronounced increases in renin and angiotensin, and secondary aldosterone excess (figs 2 and 3). Both of these patients had steep falls in arterial pressure after the initial dose of captopril. By the sixth day and subsequently blood-pressure reduction was more modest, as initial sodium deficiency, secondary aldosteronism, and plasma electrolyte abnormalities were corrected.

A contrasting type of response was seen in patients without pre-

Details of patients and results of treatment

Case No	Age and sex	Serum creatinine (μmol/l)	Renal arterial lesion (all unilateral)	Presenting blood pressure (outpatient) (mm Hg)	Basal blood pressure (inpatient) before captopril (mm Hg)	Blood pressure during treatment with captopril (mm Hg)					Blood pressure after operation (no treatment) (mm Hg)	
						two hours (inpatient)	six days (inpatient)	Long term		Operation		
								Outpatient	Inpatient		Outpatient	Inpatient
1	52 F	90	Occlusion	250/135	211/118	100/58	172/91		177/94	Nephrectomy	158/94	166/86
2	25 F	107	Stenosis	200/120	164/116	148/106	159/103	130/86	130/76	Reconstruction	134/72	125/70
3	34 F	117	Stenosis	190/130	205/108	180/88	141/87	126/76	138/79	Nephrectomy	136/84	130/71
4	54 M	300	Stenosis	220/160	229/125	206/118	205/128		185/126			
5	46 F	116	Stenosis	205/105	154/100	132/92	126/73	149/98	144/89			
6	16 M	111	Occlusion	190/120	160/108	156/98	157/83	166/94	154/83	Reconstruction	125/72	153/76
7	16 F	110	Stenosis	240/170	191/141	168/132	169/102	167/114	167/104			
8	40 M	120	Stenosis	195/135	154/107	122/82	148/93	127/77	113/64			
9	59 M	348	Stenosis	250/130	181/107	174/104	168/91	224/126	203/115			
10	52 F	79	Stenosis	260/150	220/134	138/88	163/97	130/88	191/111	Nephrectomy	156/100	161/95
11	60 M	166	Occlusion	250/130	224/127	146/96	179/99	186/102	187/94	Nephrectomy	180/96	194/109
12	52 M	124	Stenosis	180/125	213/121	158/98	180/118	146/104	142/101	Nephrectomy	177/104	179/107
13	54 F	124	Occlusion	200/120	181/102	172/108	155/92	132/88	137/92	Nephrectomy	156/104	149/95
14	58 M	133	Occlusion	200/130	217/116	179/101	162/101	212/128	215/125	Nephrectomy	202/108	166/92
15	58 M	368	Occlusion	240/125				186/94	207/97	Nephrectomy		217/101

Conversion: SI to traditional units—Creatinine: 1 μmol/l ≈ 0·01 Mg/100 Ml.

treatment electrolyte abnormalities and with a less pronounced initial increase in plasma renin and angiotensin II concentrations. One such patient (case 2) has also been reported in detail.[20] In these cases no systematic changes in exchangeable sodium or total body potassium were seen with treatment (figs 2 and 3). Some patients of this kind (cases 2 and 3) had only modest falls of pressure at two hours but showed a further slow reduction over one to three weeks of treatment; in other instances (cases 6, 7, and 8) pressures were similar during short-term and long-term treatment with captopril.

Overall, plasma sodium concentration did not change significantly by five to six weeks, though mean plasma potassium rose slightly but consistently ($p < 0.01$) (figs 2 and 3).

One man (case 4) with overall renal impairment had an inadequate fall in blood pressure (from 229/125 to 185/126 mm Hg) by the 14th day of captopril treatment, in which time exchangeable sodium had risen by 157 mmol (mEq) (fig 2). With the addition of frusemide 80 mg daily pressure fell to the range 120/80-140/95 mm Hg.

In contrast to the initial fall in blood pressure the hypotensive response during long-term captopril was not significantly related to the concomitant decrement in plasma angiotensin II concentration (systolic, $r_s = 0.44$; diastolic, $r_s = 0.14$). Serum creatinine concentration was not significantly changed during captopril treatment (initial mean $160.8 \pm$SEM 26.0 μmol/l (1.82 ± 0.29 mg/100 ml) compared with 157.9 ± 24.3 μmol/l (1.79 ± 0.27 mg/100 ml)).

The table and figs 1-3 summarise the outcome in the 10 patients who came to operation. After surgery plasma active renin concentrations had fallen steeply from the grossly raised values during captopril treatment, while plasma angiotensin II concentrations had risen slightly.

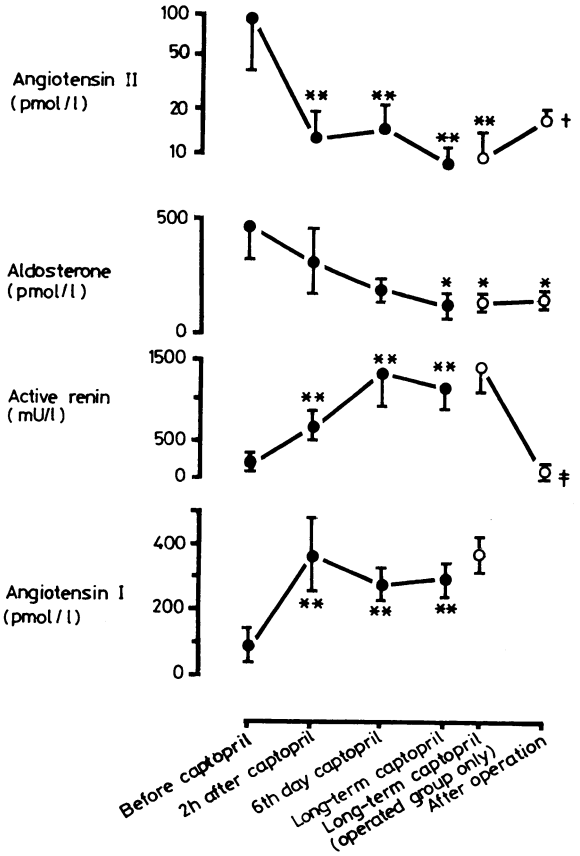

FIG 1—Mean ($\pm$SEM) plasma angiotensin II, aldosterone, and active renin concentrations and blood angiotensin I immediately before captopril, two hours after first dose, at six days, and during long-term captopril treatment. Also shown are postoperative values in 10 surgically treated patients. ● = Whole series. ○ = Operated group only.

Comparison with pretreatment values: *$p < 0.05$; **$p < 0.01$.

Comparison with five to six weeks of captopril treatment: †$p < 0.01$; ‡$p < 0.001$.

Conversion: SI to traditional units—Angiotensin II: 1 pmol/l ≈ 1pg/ml. Aldosterone: 1 pmol/l ≈ 0·4 μg/100 ml. Angiotensin I: 1 pmol/l ≈ 1·3pg/ml.

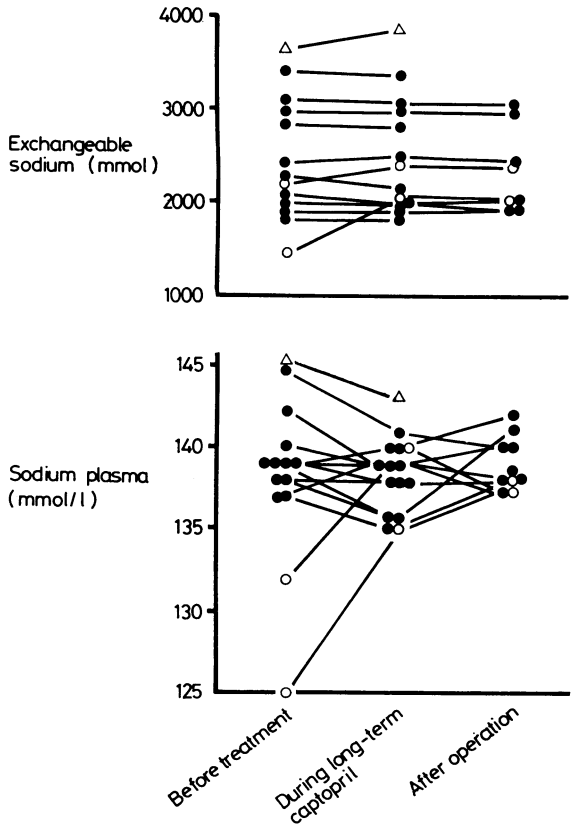

FIG 2—Total exchangeable sodium and plasma sodium concentrations before treatment, during long-term captopril treatment, and at postoperative assessment. ○ = Cases 1 and 11 with hyponatraemia, sodium deficiency, and secondary aldosterone excess before treatment. △ = Case 4 with renal impairment and hypertension resistant to captopril alone (see text).

Conversion: SI to traditional units—Sodium: 1 mmol = 1 mEq.

The variable initial fall in blood pressure with captopril has been emphasised; not surprisingly, this early response did not correlate significantly with surgical outcome (for systolic, $r_s = -0.38$; for diastolic, $r_s = -0.2$). The absolute blood pressures, however, both systolic and diastolic, observed during long-term captopril treatment were remarkably close to those seen after operation. This similarity was apparent whether inpatient or outpatient readings were compared and was irrespective of a good, modest, or poor response to surgery (table). The correlations for inpatient values were: systolic, $r_s = 0.62$; diastolic, $r_s = 0.55$; $p < 0.05$ for both.

Surgical response did not correlate significantly with pretreatment plasma active renin or angiotensin II concentration or with renal vein renin ratio but was poorer in patients with overall renal impairment (table).

Surgical treatment did not affect serum creatinine concentrations (mean $141.9 \pm$SEM 22.4 μmol/l (1.61 ± 0.25 mg/100 ml) while taking captopril; 138.0 ± 30.8 μmol/l (1.56 ± 0.35 mg/100 ml) after operation).

UNWANTED EFFECTS OF CAPTOPRIL

One patient noticed a disturbance of taste three weeks after starting captopril; this symptom remitted after a further three weeks of continued treatment. There was one case of sinus tachycardia (up to 160 beats/min) 48 hours after starting captopril. A man with overall renal impairment (case 4) developed the Guillain-Barré syndrome after five months of captopril treatment, while also receiving cimetidine and frusemide.[28] A patient with unilateral renal artery occlusion and severe overall renal impairment (case 15) developed heavy proteinuria (range 3·5-7·5 g/24 hours) nine weeks after starting captopril. Serum albumin concentration dropped to 28 g/l. Captopril was stopped and unilateral nephrectomy performed. Only ischaemic changes were observed in the glomerular basement membranes of the excised kidney, and results of fluorescence studies were negative for immunoglobulins and complement components. Two months later urine

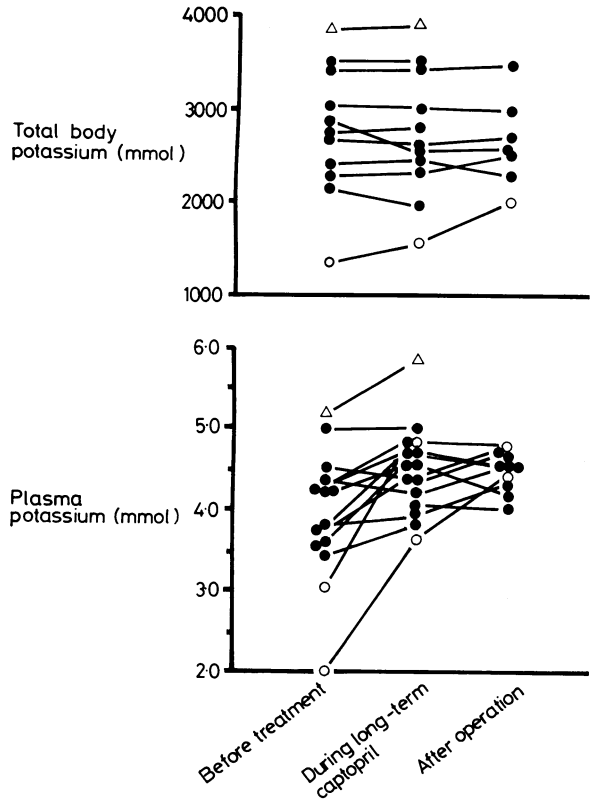

FIG 3—Total body potassium and plasma potassium concentration before treatment, during long-term captopril treatment, and at postoperative assessment. Key to symbols as in fig 2.

Concentration: SI to traditional units—Potassium: 1 mmol = 1 mEq.

protein h. d fallen to 0·8 g/24 hours and serum albumin concentration was 44 g/l. While not excluded, the nephrotic syndrome here cannot necessarily be attributed to captopril; this condition may sometimes be a feature of renal artery stenosis.[29]

Possibly if more modest doses of captopril had been employed, particularly in patients with renal impairment, the burden of side effects might have been less.[13 15 16] As mentioned, plasma angiotensin II concentrations were no lower at six days and subsequently than at two hours despite the difference in captopril dose; 150 mg thrice daily, though originally recommended by the manufacturers, could well be an unnecessarily large dose.

Discussion

In this series patients who were initially depleted of sodium and had secondary aldosterone excess corrected their sodium deficiency with captopril treatment, while those patients with an initially normal sodium state showed no change with captopril. Similarly, potassium balance was corrected by treatment when there was an initial deficiency but was otherwise not measurably altered. Presumably any natriuretic effect of the fall in plasma aldosterone[30] was offset by the loss, mainly in the unaffected kidney, of the direct natriuretic action of angiotensin II and perhaps arginine vasopressin[3 19 27 33] and by diminution of pressure natriuresis.[19 27 33] Whereas the initial hypotensive response to captopril was proportional to the immediate reduction in plasma angiotensin II concentration, this provided a poor guide either to the long-term blood-pressure reduction with captopril or to the eventual surgical outcome.

The initial hypotensive effect of captopril was greatest in those patients with sodium deficiency before treatment. Though diuretics were not used in our cases, a similar exaggerated hypotensive response to captopril would be associated with diuretic-induced sodium losses, and therefore treatment with frusemide before giving drugs such as captopril or saralasin is likely to confuse rather than facilitate diagnosis and prognosis.

The slow fall in blood pressure observed during prolonged captopril treatment in other patients of this series was consistent with antagonism of the slow pressor action of angiotensin II.[3 5 6] It remains uncertain, however, whether the hypotensive actions of captopril are the result solely of reduction of angiotensin II either within the circulation or at other sites.[13 15 24]

Our findings indicate the inadequacy of short-term inhibition of the renin-angiotensin system in forecasting surgical outcome in hypertension with renal artery stenosis. Nevertheless, prolonged use of captopril accurately predicted, in absolute terms, surgical success and failure alike. This finding requires confirmation in larger series but promises well in distinguishing the unresponsive phase 3 from the more therapeutically rewarding phase 2[4] of renovascular hypertension.

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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.

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Introduction

Inhibition of the angiotensin-converting enzyme is an effective way of lowering blood pressure,[1-3] 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.[6-8] 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