Absence of blood-pressure lowering effect of captopril in anephric patients

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Summary and conclusions

Captopril, an orally active inhibitor of angiotensin-I-converting enzyme, was administered in a single dose to five anephric patients who had extremely low plasma renin activities. The drug did not lower blood pressure or significantly alter plasma renin activity in any patient but increased mean arterial pressure slightly in three.

These results suggest that the blood-pressure lowering effect of captopril depends on an active renal renin-angiotensin system. Though additional mechanisms, such as accumulation of vasodilator kinins resulting from kininase II inhibition, may also contribute to captopril's action, these mechanisms apparently require the presence of the kidney to have a clinically detectable effect.

Introduction

Captopril (SQ 14225), an orally active competitive inhibitor of angiotensin-I-converting enzyme, is an effective antihypertensive agent in patients with essential hypertension, renovascular hypertension, and hypertension associated with renal insufficiency.¹⁻⁶ Its antihypertensive action has been attributed to blockade of the formation of the vasoconstrictor octapeptide angiotensin II.³ Additional mechanisms such as accumulation of bradykinin may play a part in the hypotensive effect, since the kinin-degrading enzyme kininase II is identical with angiotensin-converting enzyme.⁷

To test captopril's specificity of action we examined the effect of a single oral dose in five anephric patients in whom plasma renin activities were extremely low.

Patients, methods, and results

Five patients (three women and two men, aged 29-53) had undergone bilateral nephrectomy from two to 11 years before the study and were undergoing long-term haemodialysis. The reasons for nephrectomy were: uncontrollable severe hypertension in four patients (three with essential hypertension, one with progressive systemic sclerosis) and intractable renal infection in one patient (adult polycystic disease). They were all studied as outpatients while adhering to a diet containing 100 mmol (mEq) sodium and 50 mmol (mEq) potassium daily. They had no oedema and showed no clinical or radiological evidence of congestive heart failure. None were receiving vasoactive drugs. The serum concentrations of sodium, potassium, and calcium were normal in all patients. The studies were performed 24 hours after each patient's regular haemodialysis.

Captopril was administered in a single oral dose of 50 mg after blood pressure had been stable for at least half an hour with the patient in an upright, seated position. Blood pressure was measured automatically every two minutes for 30 minutes before the captopril (Arteriosonde, Roche) was given and for 90 minutes afterwards. Blood was obtained from an indwelling venous cannula immediately before and at three successive 30-minute intervals after administration

of captopril. Plasma renin activity was determined according to the method of Sealey and Laragh.⁸ Mean arterial pressure was calculated as the diastolic pressure plus one-third of the pulse pressure.

The table shows that captopril did not lower blood pressure in any patient. In three patients (cases 1, 2, and 5) the mean arterial pressure rose slightly. Plasma renin activity was extremely low in all patients and did not change substantially in response to captopril.

Effect of captopril on blood pressure, mean arterial pressure, and plasma renin activity in five anephric patients

Case No	Minutes after captopril											
	Control			30			60			90		
	BP*	MAP†	PRA‡	BP	MAP	PRA	BP	MAP	PRA	BP	MAP	PRA
1	106/70	82	0.17	120/76	91	0.22	120/78	92	0.22	118/76	90	0.22
2	100/70	80	0.30	105/75	85	0.31	110/80	90	0.31	105/80	88	0.29
3	135/70	92	0.24	140/70	93	0.28	135/70	92	0.27	135/70	92	0.27
4	160/105	123	0.08	160/105	123	0.08	160/105	123	0.07	160/105	123	0.06
5	115/40	65	0.12	105/60	75	0.12	110/60	77	0.14	108/60	76	0.13

* BP = Blood pressure in mm Hg.

† MAP = Mean arterial pressure, calculated as diastolic pressure plus one-third pulse pressure (mm Hg).

‡ PRA = Plasma renin activity (μ g angiotensin I/l/h).

Discussion

The blood-pressure lowering effect of captopril is associated with a decrease in total peripheral resistance.⁵ Reduction of circulating angiotensin II concentrations by inhibition of converting enzyme has been proposed as a major mechanism for this decrease, since the size of the vasodepressor response to captopril can be predicted by the plasma renin activity before treatment.^{2,3}

Some investigators, however, have not found a correlation between this activity and the size of blood pressure reduction by captopril,^{1,5} which suggests that captopril may act by an additional mechanism.

The mechanism most often proposed is one where an accumulation of vasodilator kinins results from inhibition of the kinin-degrading enzyme kininase II, which is identical with angiotensin-converting enzyme. Increased concentrations of circulating kinins have been reported after long-term administration of captopril to sodium-depleted dogs⁹ and after intravenous administration of nonapeptide converting-enzyme inhibitor (teprotide, SQ 20881) to patients with essential hypertension.¹⁰ Despite reductions in blood pressure, however, no increases in plasma bradykinin concentration could be detected during treatment with captopril in patients with essential hypertension⁴ or after teprotide infusion in either sodium-depleted normotensive patients¹⁰ or dogs with one-kidney Goldblatt hypertension.¹¹

Our findings support the contention that even though captopril may act by an angiotensin-independent mechanism this action depends on the presence of renal tissue. Although rabbits and sodium-depleted rats have a vasodepressor response to converting-enzyme inhibitor, this effect is absent after bilateral nephrectomy.¹²⁻¹⁴ Moreover, teprotide did not lower blood pressure in anephric patients.¹⁵ Our findings with captopril in anephric patients agree with these results.

Captopril was recently reported to have lowered blood pressure in an anephric patient,¹⁶ but to have failed to do so both when the patient was volume loaded and after he had lost 4.3 kg as a result of ultrafiltration dialysis. Mean arterial pressure rose

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slightly when captopril was given after dialysis (which we also observed in three of our patients). A third captopril test performed after he had lost a further 1.2 kg led to profound orthostatic hypotension. Although this may have been caused by captopril, nearly two hours elapsed between control pressure measurements and administration of captopril. Failure of physiological buffer mechanisms to maintain blood pressure during this period of intravascular volume depletion, rather than the action of captopril, may have been responsible for the augmented postural decline in blood pressure. In contrast, each patient in our study had a stable blood pressure in an upright, seated position for at least 30 minutes before receiving captopril.

The same authors have recently extended their studies.¹⁷ They observed reductions in blood pressure in seven anephric patients when captopril was given one hour after haemodialysis. Administering captopril 24 hours after dialysis, however, did not produce a hypotensive effect, which is consistent with our present findings. Thus the fall in blood pressure occurred only when captopril was given soon after dialysis, which suggests a mechanism related to the haemodialysis procedure. Exposure of blood to the haemodialysis membrane may have increased the production of vasodepressor kinins. If the hypotensive response was due to inhibition of kinin degradation by captopril then this response would be expected to be most evident soon after dialysis, as was observed.

Three of our patients showed an increase in mean arterial pressure after captopril. This increase ranged from 12% to 18% above the control pressure and reached a maximum 60 minutes after administration. A slight pressor effect after intravenous teprotide in some anephric patients has been observed.¹⁵ Neither the mechanism of this effect nor its importance in anephric patients or in patients with kidneys receiving captopril is known.

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SHORT REPORTS

Relation between hydrocarbon exposure and the nephrotic syndrome

Recent reports have emphasised the increased incidence and intensity of exposure to hydrocarbon solvents in patients with chronic glomerulonephritis (in particular Goodpasture's syndrome and proliferative glomerulonephritis) compared with a control population with no renal disease.¹⁻⁴ Rapidly progressive glomerulonephritis in rats exposed to petroleum vapours⁵ or fed *N,N'*-diacetylbenzidine⁶ showed that hydrocarbon-induced glomerulopathy does occur. A cause-and-effect relation between hydrocarbon exposure and human glomerulopathies based on statistical data has not been reported, however, except perhaps for the case described by Von Schéele et al.⁴ All Von Schéele's patients have had chronically deteriorating disease.

Case report

A man aged 59 years was admitted with all the signs and symptoms of a nephrotic syndrome. At work he had been exposed for prolonged periods to hydrocarbon derivatives. The figure shows the changes in proteinuria, albuminaemia, oedema, and body weight in relation to successive periods of contact with hydrocarbons and rest periods over 27 months of follow-up. The creatinine clearance remained normal, and the patient received no treatment. Clinical and laboratory investigations showed a close correlation

between a worsening of the nephropathy and exposure to toxic products at work and the complete reversal of disease activity after leaving that job.

Renal biopsy, carried out with light, immunofluorescence, and electron microscopy, showed the features of a membranous glomerulonephritis. Electron microscopy indicated that adjacent to small, probably recent, deposits on the subepithelial layer of the glomerular basement membrane were many deposits embedded in the membrane, and it also showed electron-lucent lacunae.

The course of the disease.