sooner. We now advocate that a recently head-injured patient should have a CT scan if he has either altered consciousness or other neurological signs or symptoms that do not improve after initial assessment and resuscitation. When there is a skull fracture the indications for scanning are increased; even by itself a fracture probably provides an adequate reason.

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Converting-enzyme inhibitor enalapril (MK421) in treatment of hypertension with renal artery stenosis

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Abstract

Enalapril maleate (MK421), a new inhibitor of angiotensin converting enzyme, in single daily doses of 1·25-40 mg was assessed in five patients with hypertension and renal artery stenosis. Only small falls in plasma angiotensin II concentrations were seen at doses less than 10 mg; even with 10 and 20 mg, angiotensin II concentrations had risen again 24 hours from the last dose. During long-term treatment with 10-40 mg daily all patients achieved good blood-pressure control. No significant changes of body sodium or potassium values were seen. The drug was well tolerated with no serious side effects.

These findings are evidence of the efficacy and acceptability of enalapril in the medical management of hypertension with renal artery stenosis.

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Introduction

We have reported[1] the use preoperatively of the converting-enzyme inhibitor captopril in the treatment of hypertension associated with unilateral renal artery stenosis. Long-term captopril promised well as a predictor of the blood-pressure response to operation, although this requires further study. We have also reported that oral captopril in a dose of 150 mg three times daily produces sustained suppression of the plasma angiotensin II concentration throughout 24 hours.[2] Captopril, however, has been associated with several toxic effects which may be attributable to the sulphydryl group in its molecule.[3] Although the use of lower doses of captopril may avoid at least some of these unwanted effects, it appears important to consider alternative converting-enzyme inhibitors. Enalapril maleate (MK421),[4] an orally active converting-enzyme inhibitor devoid of a sulphydryl group, may permit long-term inhibition of angiotensin II formation without incurring the side effects seen with captopril. We report preliminary results of the use of long-term enalapril in five patients with hypertension and renal artery stenosis. Particular attention was paid to the magnitude and duration of the reduction in plasma angiotensin II concentrations.

Patients and methods

Five patients (two women) aged 38-56 years gave informed consent to the study, which was approved by the hospital's ethical supervisory committee. All patients had unilateral renal artery stenosis shown by intravenous pyelography, renal arteriography, isotope nephrography,[5] bilateral renal vein renin measurements, and ureteric catheter studies.[1 6] Four had radiological evidence of atheroma and one fibromuscular hyperplasia. All had normal serum electrolyte values and renal

function (mean serum creatinine concentration 89 ± SEM 4 μmol/l; 1·0 ± 0·04 mg/100 ml). Four had had an unsatisfactory hypotensive response to beta-blocker plus diuretic, together with either hydralazine (two patients), prazosin (one patient), or minoxidil (one patient). One patient had received diuretic only with poor response. Mean outpatient blood pressure on previous treatment was 189 ± 21/105 ± 5 (SEM) mm Hg.

Patients were admitted and ate a normal ward diet. All treatment was stopped at least 14 days before enalapril was started. Placebo was given as a single morning dose for five days before active drug was administered; thereafter enalapril was given also as a single morning dose. The first three patients were the subject of a dose-finding study and began with 1·25 mg of enalapril, which was then increased to 2·5 mg, 5 mg, 10 mg, 20 mg, and 40 mg on successive days; these patients were then discharged taking 40 mg daily. After analysis of blood pressure and biochemical data in these three patients the subsequent two began treatment with 10 mg daily, which was continued for each of the six days of inpatient stay. After discharge the enalapril dose was adjusted until supine and erect blood pressures were below 140 mm Hg systolic and 90 mm Hg diastolic (phase V) four hours after the morning dose, or until a maximum dose of 40 mg daily was reached. After 12 weeks two patients were receiving 40 mg, one 20 mg, and two 10 mg daily.

Measurements of plasma active renin concentration (normal range 10-50 mU/l),[7] blood angiotensin I (2·3-15·5 pmol/l; 3-20 pg/ml),[8] plasma angiotensin II (5-35 pmol/l; 5-35 pg/ml),[9] plasma aldosterone (< 500 pmol/l; < 180 pg/ml),[10] and plasma converting-enzyme activity[11] were made after 30 minutes' recumbency before the first dose of enalapril and two, six, and 24 hours later; supine and erect blood pressure was recorded after blood sampling using the Hawksley random-zero sphygmomanometer. These measurements were repeated after 12 weeks of treatment under identical conditions. Measurements were made of total body and exchangeable sodium and potassium before and during long-term treatment.[12-14]

Data were analysed using repeated measures analysis of variance, with logarithmic transformation where appropriate. Blood pressures were compared at a total of six time points: before dosing and two and six hours later, after three months of enalapril, and at corresponding times before treatment. Concentrations of renin, angiotensins I and II, and aldosterone and converting-enzyme activity were compared at three time points: before treatment and before and two hours after daily dosing at three months. Comparisons were based on Scheffé multiple comparisons at the 1% level to guarantee an overall significance level of at most 5% for the five variables jointly.

Results

Dose-finding study—Parallel falls of plasma angiotensin II concentrations and converting-enzyme activity were apparent two hours after enalapril, increasing with increasing dosage; at all doses the effects were waning 24 hours later (figure). Blood pressure did not fall significantly during dose finding from the initial 180 ± 11/103 ± 5 mm Hg.

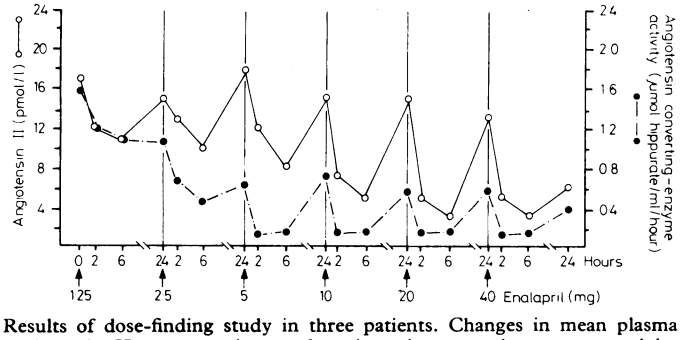
Long-term enalapril—During long-term treatment plasma converting-enzyme activity and angiotensin II concentrations were not significantly reduced 24 hours after the last dose, though active renin and angiotensin I concentrations were raised. Two hours after the morning dose renin and angiotensin I values had risen further, while plasma angiotensin II concentrations and converting-enzyme activity were significantly depressed. The mean plasma aldosterone concentration was not significantly lowered during long-term enalapril treatment (table). Despite these biochemical variations there were consistent falls in blood pressure, from average pretreatment inpatient values of 190 ± 2/101 ± 1 mm Hg supine (mean ± SEM) and 181 ± 3/105 ± 1 erect, to 144 ± 3/83 ± 1 mm Hg supine and 127 ± 4/83 ± 2 erect ($p < 0·05$ for all comparisons before treatment versus long-term treatment before and two and six hours from dosing). Neither serum sodium nor serum potassium values were significantly altered by long-term enalapril (respective means ± SEM 142 ± 0·5 and 3·8 ± 0·1 mmol(mEq)/l before treatment, and 142 ± 0·7 and 4·1 ± 0·2 mmol/l during treatment). Similarly exchangeable sodium (102·2 ± SEM 2·5% of predicted normal versus 97·8 ± 2·9%), exchangeable potassium (99·1 ± 2·5% versus 100·2 ± 1·6%), total body sodium (103·5 ± 4·5% versus 100·5 ± 4·2%), and total body potassium (103·2 ± 4·5% versus 101·2 ± 3·1%) were not significantly changed. There was a slight but significant ($p < 0·05$) increase in serum creatinine concentration with long-term treatment (mean 89 ± SEM 4 to 115 ± 7 μmol/l; 1·0 ± 0·05 to 1·3 ± 0·08 mg/100 ml).

Mean (± SEM) changes in components of renin-angiotensin system during treatment with enalapril

	Placebo*	After three months of enalapril	
		Immediately before daily dose	Two hours after morning dose
Renin (mU/l)	69 ± 17	912 ± 549†	1687 ± 570†
Angiotensin I (pmol/l)	14·7 ± 4·2	88 ± 33†	206 ± 66†
Angiotensin II (pmol/l)	24 ± 6·3	13 ± 3·0	8 ± 1·9†
Aldosterone (pmol/l)	272 ± 83	133 ± 33	183 ± 33
Angiotensin converting-enzyme activity (μmol hippurate/ml/hour)	1·5 ± 0·33	0·71 ± 0·07	0·17 ± 0·05†

*Placebo values immediately before first dose of enalapril at start of treatment.
†$p < 0·05$ compared with placebo value.
Conversion: SI to traditional units—Angiotensin I: 1 pmol/l ≈ 1·3 pg/ml. Angiotensin II: 1 pmol/l ≈ 1 pg/ml. Aldosterone: 1 pmol/l ≈ 0·04 ng/100 ml. Angiotensin converting-enzyme activity: 1 μmol hippurate/ml/hour ≈ 179 μg hippurate/ml/hour.

Side effects—No serious side effects were encountered. One patient developed tachycardia in the standing position; supine and erect pulse rates rose from 72 and 73 during the placebo period to 82 and 129 at one week and 79 and 107 at three months. The same patient noted worsening of pre-existing Raynaud's phenomenon. In all cases enalapril was associated with an increased feeling of wellbeing, and one man recovered previously impaired sexual function. No instances of disturbance of taste, rash, leucopenia, glycosuria, or proteinuria were encountered.



Results of dose-finding study in three patients. Changes in mean plasma angiotensin II concentrations and angiotensin converting-enzyme activity with increasing daily dosage of enalapril.
Conversion: SI to traditional units—Angiotensin II: 1 pmol/l ≈ 1 pg/ml. Angiotensin converting-enzyme activity: 1 μmol hippurate/ml/hour ≈ 179 μg hippurate/ml/hour.

Discussion

None of these patients has required an operation. Thus proof of the role of the renal artery lesion in causing hypertension is lacking, and we cannot comment on the value of long-term enalapril as a guide to surgical outcome.

Enalapril is more powerful and sustained in its action than captopril.[15] Captopril, given as 150 mg three times daily, does suppress the plasma angiotensin II concentration over 24 hours.[2] Studies in healthy volunteers[16] show that, given acutely in a single daily dose of 20 mg, enalapril does not fully suppress plasma angiotensin II over 24 hours. Our results suggest similar lack of complete suppression with long-term use. Nevertheless, blood pressure remained well controlled at all times studied during prolonged treatment; indeed, the lower blood pressure seen in every patient during long-term treatment than in the first week might in part result from elimination of the slow pressor action of angiotensin II.[17]

These preliminary findings thus provide evidence of the efficacy and tolerability of enalapril in the medical treatment of hypertension with renal artery stenosis.

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Early prognosis of epilepsy

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Abstract

In 94 previously untreated new referrals to a neurological clinic with tonic-clonic or partial seizures or both the failure rate for optimum single-drug treatment with phenytoin or carbamazepine after a median of 32 months was 17%. Failure of single-drug treatment was associated especially with the presence of additional neuropsychiatric handicaps but also with partial or mixed seizures, symptomatic epilepsy, and a higher number and frequency of tonic-clonic or partial seizures before treatment. Analysis of the recurrence of seizures suggested that the first year of treatment may be crucial in determining the long-term prognosis.

These findings are in keeping with the concept that seizures may predispose to further seizures, and imply that early, effective treatment may be important to prevent evolution into chronic and more intractable epilepsy.

Introduction

Epilepsy is usually a chronic disorder with a widely varying outcome.[1-3] There has been little prospective study, however, of the factors that influence prognosis.[3] Rodin[1] in his detailed review commented that most reports were retrospective surveys of selected groups of patients with chronic epilepsy who had gravitated to institutions or hospital clinics, often with inadequate documentation and follow-up.

In the past six years we have undertaken studies of single-drug treatment with either phenytoin or carbamazepine, in which we have monitored drug concentrations, in new referrals to a neurological clinic with previously untreated tonic-clonic or partial seizures, or both. In addition to the pharmacological aspects already reported[4-7] this has given us the opportunity of studying for the first time, prospectively and from the onset of epilepsy, factors that influence the prognosis for control of seizures.

Patients and methods

We studied 106 consecutive referrals to a neurological clinic with tonic-clonic or partial epilepsy, or both, who had not been treated previously, had no progressive cerebral disorder, and had had two or more recent tonic-clonic seizures or sufficient partial seizures to warrant treatment. Details of the treatment regimen with either phenytoin or carbamazepine and of the blood concentration monitoring have been reported previously.[4-6] Our policy was to begin with a small dose of one drug, monitor the blood concentration of the drug at each clinic visit, and increase the dose by small increments, if necessary into the optimum range of blood concentrations for that drug as dictated clinically by the recurrence of seizures, except where there was evidence that the recurrence was due to poor compliance. Two or more seizures despite blood drug concentrations in the optimum range were regarded as evidence of failure of single-drug treatment. Optimum drug concentrations were phenytoin 40-80 μmol/l and carbamazepine 16-32 μmol/l.

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