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Intravenous captopril treatment in patients with severe cardiac failure

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SUMMARY The effect of intravenous captopril was studied in 26 patients with severe chronic heart failure. Fourteen patients received a 25 mg intravenous bolus dose and 12 patients were given a series of incremental intravenous doses over the range 0·3125–45 mg. After the 25 mg bolus dose there was a rapid reduction in systemic vascular resistance and systemic blood pressure. The effect was greatest five minutes after the dose when cardiac output was increased by 20%. Mean right atrial pressure and pulmonary end diastolic pressure fell more slowly and reached their nadir 60 minutes after administration. Plasma free captopril concentration was significantly correlated with percentage reduction in systemic vascular resistance 15 minutes after the bolus injection, but was not correlated with either changes in right atrial or pulmonary artery pressures. With the series of incremental doses there was a progressive fall in systemic vascular resistance until a cumulative dose of 5·0 mg was reached; beyond this there was no further significant change.

The rapid response to intravenous captopril indicates that it may be useful in the treatment of patients with severe heart failure who require intensive treatment. After intravenous injection of captopril haemodynamic responses in patients with heart failure were greatest at plasma concentrations of 100 g/ml to 150 ng/ml. This is considerably higher than the plasma free captopril concentrations found after conventional oral doses of captopril.

Captopril, an angiotensin converting enzyme inhibitor, has become established as a treatment for severe chronic cardiac failure.[1–5] Until now only oral formulations have been available for clinical studies. To assess the feasibility of intravenous captopril treatment in patients with severe heart failure we have studied the haemodynamic responses to the administration of (*a*) a 25 mg bolus dose of intravenous captopril and (*b*) a series of incremental intravenous doses. The haemodynamic responses were compared with the time-profile of changes in plasma free captopril concentration and plasma renin activity.

Patients and methods

PATIENTS

We studied 26 patients (17 men and 9 women, mean age (SE) 60 (2) years, range 36–76). Fourteen received a bolus dose and 12 were given incremental doses. All patients had breathlessness at rest or on mild exertion (New York Heart Association functional class III or IV) despite regular treatment with digoxin and diuretic (frusemide $\geqslant$120 mg/day or bumetanide $\geqslant$4 mg/day). Each patient had severe myocardial impairment; this was secondary to ischaemic heart disease in 17 patients, to cardiomyopathy in six, and to rheumatic heart disease in three patients. The isotopically determined left ventricular ejection fraction (mean (SE)) was 19 (2)% (range 6–38%). Patients had fasted overnight and had not taken other medications on the day of study. Vasodilator treatment had been stopped at least three days before.

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HAEMODYNAMIC RECORDINGS

The patient remained supine throughout the study period. Right atrial and pulmonary arterial pressures and cardiac output were measured with a triple

lumen flow directed thermodilution catheter. Zero for pressure recordings was taken at 10 cm above table height. Cardiac outputs were measured in triplicate. Systemic arterial pressure was recorded at the arm by an electronic sphygmomanometer (Copal digital sphygmomanometer: UA251).

PLASMA FREE CAPTOPRIL CONCENTRATION

N-ethylmaleimide (10 mg) was added to 5 ml plasma which had been separated in a refrigerated centrifuge immediately after withdrawal of the blood sample. Plasma free captopril concentration was measured by radioimmunoassay.[6] The coefficient of variation of the assay is 7·5% with a minimum detection limit of 2 ng/ml in plasma.

PLASMA RENIN ACTIVITY

Plasma renin activity was measured by the method of Drury and Edwards.[7] The normal range for supine subjects is 0·3–1·5 ng/ml/h.

BOLUS INTRAVENOUS CAPTOPRIL DOSE

A 25 mg bolus dose of captopril was given to 14 patients. Each had tolerated a 6·25 mg oral test dose three days earlier. After the insertion of the thermodilution catheter and after haemodynamic measurements had stabilised, three control recordings were made at 15 minute intervals. The 25 mg dose of intravenous captopril was then injected at a constant rate over 5 minutes. Haemodynamic recordings and blood samples for plasma free captopril concentration and plasma renin activity were taken at 5, 15, 30, 45, 60, 75, and 90 minutes after the end of injection. An additional measurement of systemic arterial pressure was taken at 2·5 minutes.

INCREMENTAL INTRAVENOUS CAPTOPRIL DOSES

After control recordings, 12 patients received bolus doses of 0·3125, 0·3125, 0·625, 1·25, 2·5, 5·0, and 10·0 mg of captopril at 15 minute intervals, corresponding to cumulative dosages of 0·3125, 0·625, 1·25, 2·5, 5·0, 10·0, and 20·0 mg of captopril. Four patients received an additional final 25 mg dose of captopril. Each dose was injected over 30 seconds. Haemodynamic recordings and blood samples were taken immediately before each incremental dose of captopril.

STATISTICAL ANALYSIS

The following statistical tests were performed on a PDP11/44 computer with Minitab statistical package: Student *t* tests, analysis of variance, and correlation coefficients. All figures are mean (SE).

Results

Figure 1 shows the haemodynamic changes found after the 25 mg intravenous bolus dose. Systemic vascular resistance, mean systemic arterial pressure, and cardiac output changed rapidly, with maximal changes occurring at five minutes after the dose. Pulmonary end diastolic pressure and mean right atrial pressure fell more slowly reaching a nadir at 60 minutes after captopril. The Table shows the means of individual maximum changes. Plasma free captopril concentration was 2106 (417) ng/ml at 5 minutes after end of injection and fell to 75 (12) ng/ml at 90 minutes. The plasma free captopril concentration and percentage reduction in systemic vascular resistance were significantly correlated at +15 minutes ($r=0·60$, $p=0·02$). The plasma free captopril concentration and percentage reduction in mean right atrial pressure were not significantly correlated.

Figure 2 shows the haemodynamic response and plasma free captopril concentration after each incremental dose. There was a progressive change in systemic vascular resistance up to a cumulative dose

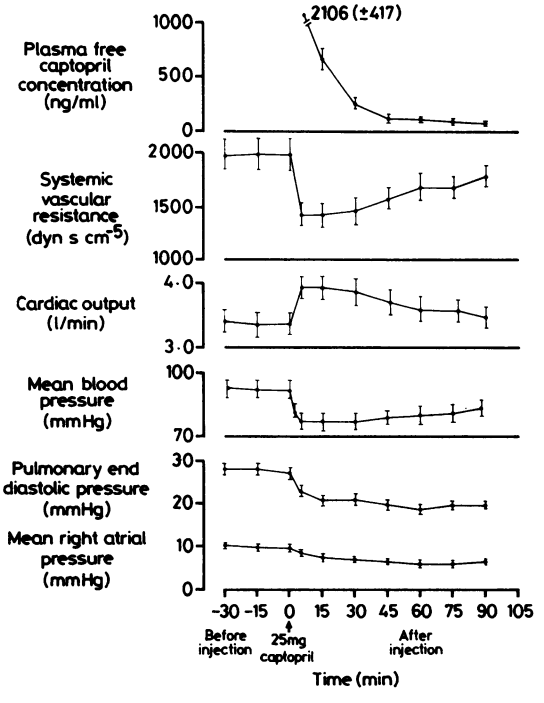

Fig. 1 *Time profile of mean (SE) haemodynamic response after a 25 mg intravenous bolus dose of captopril was injected over 5 minutes in 14 patients with severe chronic heart failure. (Time 0, end of injection.)*

Table *Maximal haemodynamic changes after a 25 mg intravenous bolus dose of captopril in 14 patients (mean (SE))*

	Basal	*Maximal change*	*% change*	*p value**
Systemic vascular resistance (dyn s cm^{-5})	1994 (138)	1380 (100)	−31%	<0·001
Mean systemic pressure (mm Hg)	93 (4)	76 (4)	−18%	<0·001
Cardiac output (l/min)	3·43 (0·18)	4·11 (0·22)	+20%	<0·001
Pulmonary artery end diastolic pressure (mm Hg)	25 (2)	18 (2)	−28%	<0·001
Mean right atrial pressure (mm Hg)	10·2 (1·1)	5·9 (1·1)	−42%	<0·001
Heart rate (beats/min)	86 (5)	77 (5)	−10%	<0·001

*Analysis of variance.

of 5 mg; beyond this no further significant change was recorded (analysis of variance). The four patients given an additional final dose of 25 mg captopril (total cumulative dose 45 mg) did not have any further change with this additional dose (data not shown).

Six patients given a 25 mg intravenous bolus dose had plasma free captopril concentration and plasma renin activity measured for up to 24 hours after the dose (Fig. 3). The half life for plasma free captopril measured between 1·5 and 8 hours was 3·36 (0·25) h. Volume of distribution was 3·96 (0·53) l/kg and the clearance was 0·81 (0·07) l/kg/h. In these six patients plasma renin activity rose from a mean control value of 9·1 (3·7) ng/ml/h to a maximum of 65·6 (25·4) ng/ml/h 45 minutes after the injection of a 25 mg bolus ($p < 0·05$).

Discussion

An intravenous bolus of 25 mg captopril produced a very rapid reduction in systemic vascular resistance and caused almost immediate changes in cardiac output and systemic blood pressure. This is in keeping with the fact that angiotensin converting enzyme is located principally in the body's central compartment, that is the blood and lungs. The reduction in mean right atrial pressure and pulmonary end diastolic pressure was biphasic with a rapid initial fall followed by a continued decline to the nadir at 60 minutes after injection. This finding supports the concept that the effect of captopril on venodilatation may not be identical to the effect on systemic resistance.[8-12] The rapid response to intravenous doses indicates that intravenous captopril may have

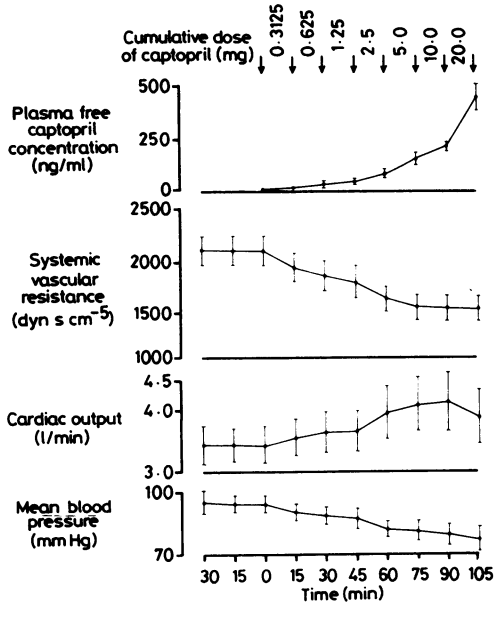

Fig. 2 *Profile of mean (SE) haemodynamic response after incremental doses of intravenous captopril in 12 patients with severe chronic heart failure.*

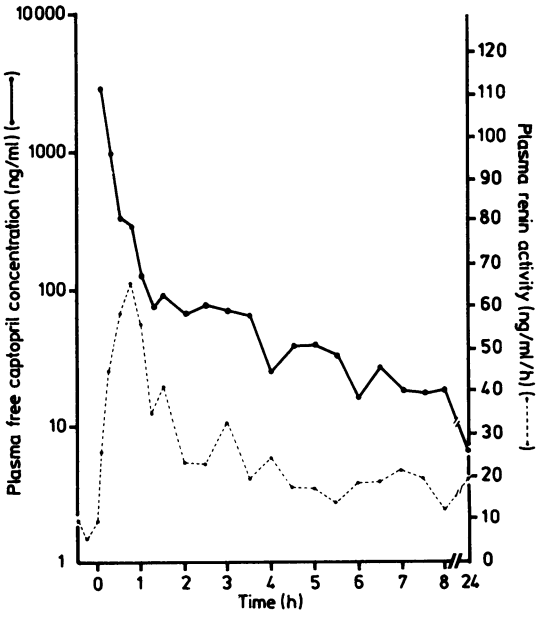

Fig. 3 *Plasma free captopril concentration and plasma renin activity after a 25 mg intravenous dose of captopril in six patients with severe chronic heart failure.*

a place in the treatment of patients with heart failure who require intensive treatment.

The results of the incremental dosage study indicate that in patients with heart failure there is a progressive increase in response between 0·3125 mg and 5·0 mg of intravenous captopril and that a dosage range of 0·5–5·0 mg could be used to titrate the response in patients on intravenous treatment. Preliminary work in patients with hypertension suggest that they have a different dose response relation.

The effects of the 25 mg bolus of captopril on systemic vascular resistance, cardiac output, and systemic pressure were not sustained at the maximum level and the reduction in systemic vascular resistance fell from 28% to 9% by 90 minutes after the dose. Mean plasma free captopril concentration had fallen to 75 ng/ml by then. In the patients receiving incremental doses the plateau of response was reached at a mean plasma free captopril concentration of 128 ng/ml. This suggests that a maximal haemodynamic response to captopril in patients with heart failure may require plasma free captopril concentrations in the range of 100–150 ng/ml. This is considerably higher than the plasma free captopril concentration found before dosage in cardiac patients maintained on 12·5–25 mg of captopril given orally three times a day.[13] Though it is difficult to correlate the short term haemodynamic response and long term response to captopril, these data suggest that a higher dose or more frequent administration of captopril may be needed to maintain a maximal haemodynamic response.

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