LONG TERM EFFECT OF CAPTOPRIL IN HYPERTENSION WITH CHRONIC RENAL FAILURE

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Summary

We report the use of the orally active converting enzyme inhibitor Captopril in hypertensive patients with mild chronic renal failure. Twenty eight patients were followed for a period of six months. Eleven patients required the addition of furosemide. Mean arterial pressure (MAP) decreased in all but two at six months (MAP: 102 ± 0.8 vs 133 ± 2.2mmHg, p < 0.001).

Untoward effects were frequent: the commonest reactions are loss of taste (four patients), skin rashes (11 patients), proteinuria (2 patients), tachycardia (2 cases). These side effects disappeared after reduction of dose (10 cases) or withdrawal (8 cases).

Patients on 300mg daily or less were free of any untoward effect.

In summary (i) Captopril alone or in combination with furosemide has an antihypertensive effect in patients with chronic renal failure and hypertension; (ii) side effects seem to be dose dependant and a reduced dosage should be used in these patients.

Introduction

Sodium seems to play an important role in hypertension associated with chronic renal failure. Despite low or normal renin levels in these patients, a deranged relationship between body sodium-volume state and circulating renin has been described. These renin levels, though seemingly normal, may be inappropriate in relation to the associated sodium retention [1].

The development of a new orally active converting enzyme inhibitor Captopril (or SQ14225) made possible a long term study in these patients [2].

We report our clinical experience of Captopril in the treatment of 28 hypertensive patients with mild chronic renal failure.
Patients and methods

Patients

Twenty-eight hypertensive patients aged 18–67 (average 48) with chronic renal failure (serum creatinine levels 140–250μmol/L) were studied. All had undergone intravenous pyelography and 15, renal biopsy. Aetiology of renal impairment were nephroangiosclerosis (n = 10) chronic interstitial nephritis (n = 8) chronic glomerulonephritis (n = 8) and scleroderma (n = 2).

Procedure

All patients had been on antihypertensive therapy. Despite treatment diastolic blood pressure averaged 110mmHg. Antihypertensive therapy was discontinued at least four days before Captopril was given. Patients were admitted to hospital and put on a fixed diet containing 100mmol sodium and 60mmol potassium per day. On the morning of the third hospital day 25mg of Captopril were given three times a day. Thereafter the dose was progressively increased to 150mg three times a day. On the eighth hospital day patients were discharged. Eleven of them required additional diuretic therapy (80–500mg furosemide orally) one month after starting treatment with Captopril.

Blood samples for routine chemistry were taken one day before and five days after starting treatment, and monthly thereafter.

Plasma renin activity [3] and plasma aldosterone [4] were determined by radio-immunoassay: samples were taken one day before and five days after starting treatment. Renin classification was based on the 24 hours urinary sodium excretion.

Data were analysed by the Student’s paired t-test.

Results

Antihypertensive effect of Captopril (Figures 1 and 2): five days after starting treatment, mean arterial pressure (MAP) fall from 135 ± 2.2mmHg to 122 ± 2 mmHg (p < 0.01). Thereafter Captopril reduces progressively MAP reaching the optimum effect at two months (103 ± 0.9, p < 0.001). At six months, the dose of Captopril averaged 300mg per day for the 20 remaining patients. Eleven patients required addition of furosemide: MAP decreased in all these patients but two. Mean body weight (62 ± 5 vs 63 ± 8kg) and mean heart rate (74 ± 2 vs 76 ± 3b/mn) remained unchanged.

Mean serum potassium rose from 4 ± 0.3 to 4.7 ± 0.4mmol/L (p < 0.05). Mean serum creatinine remained unchanged (210 ± 10 vs 220 ± 15μmol/L), but five patients improved their renal function and two experienced a rise of serum creatinine.

Untoward effects (Figure 3): The commonest reactions were maculo-papular rashes (n = 9) which cleared on withdrawal (n = 3) or reduction of dose (n = 6), loss of tase occurred in four patients, and required withdrawal in two. Two
Figure 1. Effect of Captopril on mean arterial pressure (MAP). MAP expressed in mmHg (mean ± SEM). n = number of patients; w = weeks; c = control; * = p < 0.01; ** = p < 0.001

Figure 2. Long term treatment by Captopril: results at six months. [ ] Success: diastolic blood pressure less or equal to 95mmHg. [ ] Failure: diastolic blood pressure more than 95mmHg. [ ] Withdrawal: patients with severe side effects requiring withdrawal of Captopril. N = number of patients; + Furosemide: patients requiring addition of furosemide
patients experienced both rash and loss of taste. Severe proteinuria (more than 3g/day) occurred in two patients associated with a rise of serum creatinine four months after starting treatment by Captopril. After withdrawal both renal function and proteinuria were improved. One patient with rheumatoid purpura (male, 30 years old) associated with severe hypertension and mild renal failure (serum creatinine: 350µmol/L) died suddenly. Captopril was effective in lowering blood pressure (150/90mmHg) after three weeks treatment without untoward effect in this patient; he died suddenly at home after severe lumbar pain but necropsy was not performed.

Serum potassium rose in all patients but remained within the normal range: we did not see any severe hyperkalaemia. Tachycardia occurred in two cases requiring addition of Atenolol in one case, the other patient stopped Captopril by himself.

All patients on 450mg daily experienced at least one side effect. Conversely patients without any side effects averaged 230mg/day. All the successfully treated patients at six months were given 300mg of Captopril or less daily.

In summary, one patient died suddenly, seven patients experienced severe untoward effects requiring withdrawal, 10 patients experienced mild reactions which disappeared on reduction of dose. Ten patients remained without any unwanted effects.
Discussion

Our results are in agreement with previous findings obtained [5] in patients with chronic renal failure. Several mechanisms could explain this hypotensive action of Captopril.

(i) Specific angiotensin inhibition, exposing the inappropriate renin response and the sodium retention that exists in patients with hypertension and chronic renal failure. (ii) Captopril could potentiate the vasodilating effect of the Kallikrein-kinin system which may be involved in the pathogenesis of hypertension with renal failure [6]. (iii) Captopril may have another non specific antihypertensive effect [7].

In patients with essential hypertension untoward effects were frequently reported [8, 9]: the commonest reactions were skin rash, loss of taste, proteinuria, tachycardia, renal failure. Unwanted effects occurred in 64% of our patients. These reactions were severe enough to require withdrawal in 20% of cases. The high frequency of side effects does not agree with a previous report in patients with chronic renal failure [5] showing only one skin rash in eight patients on 400mg per day or more.

The sudden death reported by us does not seem necessarily to have been induced by Captopril.

Obviously the high frequency of side effects seems to be dose-related: (i) 80% of Captopril ingested is excreted in the urine [10]; (ii) all our patients on 450mg/day experienced at least one side effect; (iii) patients taking 300mg/day or less did not experience any untoward effect.

Conclusion

Captopril is useful in the treatment of severe hypertension in patients with mild chronic renal failure. Untoward effects are infrequent if careful dosage is used.

For these patients we suggest the following protocol:

(i) starting dose 25mg three times daily progressively increased to a maximum of 100mg three times daily;
(ii) wait two months to appreciate the optimum effect;
(iii) add diuretic if diastolic blood pressure is more than 95mmHg.

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