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CAPTOPRIL IN ESSENTIAL HYPERTENSION

E. RABINAD ESTRADA, M. INGELMO MORIN, A. MARTINEZ AMENOS, J. ALSINA & A. BALCELLS GORINA

Department of Internal Medicine, Hospital Clinico y Provincial and Servicio Nefrologia, Ciudad Sanitaria 'Principes España', Barcelona, Spain

1 Forty-one patients with essential hypertension, stages I, II, and III, were treated with captopril alone or in combination with hydrochlorothiazide. Forty two percent were responsive to captopril alone, while the remaining 58% also required the diuretic. The need for the diuretic was related to the phase of hypertension.

2 There was no significant relation between drug response and plasma renin activity. Serum concentrations of creatinine and potassium remained normal, and there were no pathological changes in serum glucose, cholesterol, uric acid concentrations, erythrocyte count, packed cell volume, haemoglobin, or heart rate.

3 Captopril was well tolerated. One patient developed a rash and another ageusia, which disappeared spontaneously. A third, who was also taking allopurinol, developed leucopenia but it disappeared after treatment was withdrawn. There were no cases of proteinuria attributable to captopril; and proteinuria disappeared in four of five patients who were proteinuric before the start of treatment.

4 These findings suggest that doses of captopril of 150 mg to 300 mg (with or without a diuretic) may be adequate for controlling the blood pressure of most patients with essential hypertension.

Introduction

In this study of captopril in essential hypertension captopril was used alone or associated with a diuretic. Since the patients studied were all out-patients, it is difficult to assess whether they all followed a very strict low-sodium diet. Most of our patients came to us from other centres for examination and treatment or simply because their blood pressure could not be reduced with conventional therapy.

Methods

Forty-five patients, 15 men and 26 women, entered the study; four of them dropped out for different reasons. Their mean age was 48 ± 7 years. Before starting treatment with captopril their blood pressure was 192 ± 27/112 ± 15 mm Hg. According to the World Health Organisation classification: 14 patients (34%) had stage I hypertension, 21 (51%) stage II, and six (15%) stage III.

The presence of secondary hypertension was excluded in all patients through the conventional protocol for the study of hypertension, which includes basic clinical and biological studies, intravenous urography, and the systematic determination of plasma cortisol and aldosterone concentrations as well as the urinary excretion of catecholamines and metanephrine. Plasma renin activity was determined at pH 7.4; we considered patients to have low-renin hypertension if they lacked plasma renin activity stimulation (normal values: 1.2 ± 0.5).

The clinical and biological studies were performed over a period of six to twenty months (once a week during the first month, once every fortnight up to four months, and once a month afterwards). Supine blood pressure and pulse rate were determined after ten minutes and that of standing blood pressure rate after two minutes.

We used increasing doses of captopril and, if necessary, we added a diuretic until satisfactory blood pressure was achieved. After a washout period of 10 days initial doses were 25 mg every eight hours over two weeks. If the response was not satisfactory, doses were increased to 50 mg every eight hours for a further two weeks. If there was still little response 50–100 mg/day of hydrochlorothiazide was added to the 150 mg of captopril, then the dose was increased to 300 mg/day of captopril plus hydrochlorothiazide and up to 400 mg/day of captopril plus hydrochlorothiazide.

Results

In terms of reduction of blood pressure six patients (15%) responded satisfactorily to 75 mg/day; 11 (27%) to 150 mg/day; 11 (27%) to 150 mg/day plus

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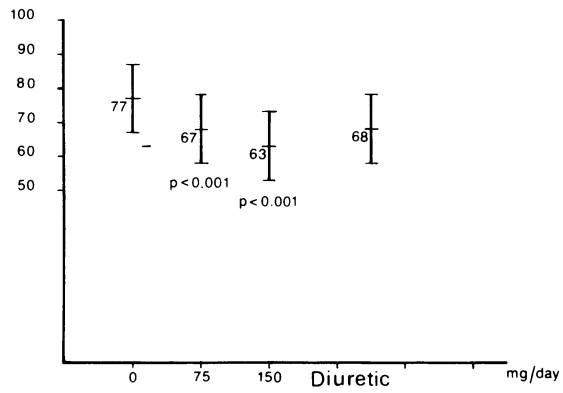

Figure 1 Change in heart rate on captopril.

hydrochlorothiazide; eight (19%) to captopril 300 mg/day plus hydrochlorothiazide; and five (12%) to the maximum dosage of 400 mg of captopril per day plus hydrochlorothiazide. The mean blood pressure changed from 192 ± 27/112 ± 15 mm Hg to 140 ± 15/90 ± 8 mm Hg ($p < 0.001$).

With the increase in the dose of captopril a statistically significant reduction in heart rate was observed, which in no case was less than 60 beats/min. (Figure 1). Heart rate was 77 beats/min before the onset of treatment, 67 beats/min with 75 mg/day, and 63 beats/min with 150 mg. When a diuretic was added to 150 mg, 300 mg, and 400 mg of captopril an increase in heart rate was observed.

No significant differences in plasma renin activity were observed in the response to captopril. Of the 41 patients who entered the study 25 were considered to have low-renin hypertension. In 12 (48%) of these patients a satisfactory response was obtained with doses of 75–150 mg. Thirteen patients (52%) required higher doses of captopril together with 50–100 mg of hydrochlorothiazide. Of the remaining 16 patients, who were considered to have normal or high-renin hypertension, five (31%) were responsive to doses of 75 or 150 mg. In 11 patients (69%) it was necessary to use higher doses and 50–100 mg of hydrochlorothiazide.

Overall 42% of the patients treated were responsive to captopril alone and the remaining 58% required higher doses together with a diuretic. The variation in plasma renin activity before and after treatment was statistically significant, rising from 0.7 ± 0.5 to 2.57 ± 3.95 ($p < 0.05$). The patients in whom plasma renin activity could not be stimulated with frusemide (80 mg) and orthostatism over two hours were considered to have low-renin hypertension.

Table 1 shows the response to captopril alone and the need for the use of increasing doses and a diuretic in relation to the stage of hypertension. While most of stage I patients were responsive to captopril alone, this proportion rose to 67% with stage II hypertension and to 84% with stage III.

All the patients studied had a normal renal function (serum creatinine 94.5 ± 33.0 mmol/l). At the end of the study these values remained normal. Only a small though significant decrease ($p < 0.05$) was observed (Table 2). Serum potassium values were also within normal range. Five patients had proteinuria before treatment with captopril. One of the patients was still proteinuric at the end of the study, while proteinuria disappeared in the remaining patients.

Side effects occurred in three patients. One developed a rash which remitted spontaneously without requiring a reduction in dose. One patient developed transient ageusia, which also remitted spontaneously without withdrawal of treatment. The third patient, who was also taking allopurinol, developed transient leucopenia. This disappeared after withdrawal of allopurinol and captopril.

Discussion

Our clinical study of 41 patients has shown that captopril is an effective drug for treating essential hypertension, stages I, II, and III. Forty-two percent of the patients were responsive to captopril alone, while the remaining 58% required a diuretic as supplemental therapy. The need for the use of a diuretic was related to the stage of hypertension.

There was no significant relation between drug response and plasma renin activity. Serum concentrations of creatinine and potassium remained normal,

Table 1 Therapeutic response of the 41 patients according to their World Health Organisation classification

	Stage I	*Stage II*	*Stage III*	*Total*
Captopril alone	9	7	1	17
Captopril plus diuretic	5 (35%)	14 (67%)	5 (84%)	24
Total	14	21	6	41

$p < 0.05$.

Table 2 Changes in serum creatinine and potassium

	Before captopril	*After captopril*	p *value*
Creatinine (mmol/l)	94.5 ± 33.0	84.2 ± 31.1	< 0.05
Potassium (mmol/l)	4.1 ± 0.5	4.4 ± 0.4	< 0.001

and there were no pathological changes in serum glucose, cholesterol, uric acid concentrations, erythrocyte count, packed cell volume, or haemoglobin. The heart rate also did not show any pathological changes. Captopril was well tolerated. We observed only one case of rash and another of dysgeusia, which disappeared spontaneously. A third patient, who was also taking allopurinol, developed leucopenia, but it remitted after cessation of the treatment. Not a single case of proteinuria attributable to captopril was observed and it is worth mentioning that proteinuria disappeared in four or five patients who were proteinuric before treatment was started.

To establish the final role of captopril in the treatment of essential hypertension it will be necessary to have a much longer follow-up, and to see whether captopril is able to reduce complications due to hypertension and side effects observed with other conventional antihypertensive agents. We believe that doses of 150 to 300 mg (with or without diuretic) may be adequate for controlling the blood pressure of most patients with essential hypertension.