Low-Dose Captopril Therapy in Mild and Moderate Hypertension
Randomized Comparison of Twice Daily vs Three Times Daily Doses

LUIGI COREA, M.D., MAURIZIO BENTIVOGLO, M.D., AND PAOLO VERDECCHIA, M.D.

SUMMARY We have investigated the antihypertensive activity of relatively low daily doses of captopril in patients with mild and moderate arterial hypertension. In a first trial, at the end of a 2-week placebo washout period, 18 patients with essential hypertension WHO Stage I or II were treated with captopril, 25 mg three times daily (t.i.d.), 25 mg twice daily (b.i.d.), 50 mg t.i.d., and 50 mg b.i.d., according to a randomized within-patient open design, with each regimen lasting for a 2-week period. In a second trial, 12 hypertensive patients not adequately controlled by chlorthalidone 25 mg daily as monotherapy (supine diastolic blood pressure at rest > 95 mm Hg), continued the diuretic treatment in combination with captopril, 25 mg t.i.d. and 25 mg b.i.d. according to a randomized within-patient open design.

Analysis of variance did not reveal differences between the four captopril dosing schedules (1st trial), or between the two captopril dosing schedules (2nd trial). Both the patients on captopril monotherapy (1st trial) and those cotreated with chlorthalidone (2nd trial) showed lower systolic and diastolic blood pressure values on each captopril regimen compared to prerandomization values (all p < 0.01). No relevant unwanted effects were noted. We conclude that in patients with mild or moderate essential hypertension, either untreated or resistant to chlorthalidone, captopril is effective in reducing blood pressure even at daily doses not exceeding 150 mg, without differences between a t.i.d. and a b.i.d. dosing schedule. (Hypertension 5 (suppl III): III-157-III-159, 1983)

KEY WORDS • hypertension • captopril • compliance

In most studies reported so far, captopril has proved effective in the management of arterial hypertension, particularly in patients not adequately controlled by other available drugs. The occurrence of unwanted effects, albeit relatively rare, has somewhat restricted the clinical use of captopril, so that there are few clinical reports on the antihypertensive efficacy and tolerability of this agent in patients with mild or moderate hypertension. It has been suggested that the large captopril doses used in most studies may have contributed, at least in part, to the unwanted effects and that a reduction in the dose could be expected to improve the tolerability of the drug.

This study was designed to evaluate the antihypertensive efficacy and tolerability of different relatively low doses of captopril in patients with mild or moderate essential hypertension, either resistant to diuretic therapy or treated with captopril as monotherapy.

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Methods

We conducted two separate trials according to the protocols described below. All patients gave their full informed consent.

Trial 1

A 2-week placebo washout period, preceded by gradual discontinuation of previous antihypertensive treatments, was carried out in 18 outpatients with essential arterial hypertension WHO Stage I or II (10 men and 8 women with a mean ± sd age of 49.7 ± 9 years). They were then treated with captopril in four different daily dosing schedules according to a randomized within-patient open design. The four different captopril schedules were as follows: 25 mg thrice daily (t.i.d.), 25 mg twice daily (b.i.d.), 50 mg t.i.d., and 50 mg b.i.d. Each schedule was administered over a 2-week period without intervals between the periods. Admission to the Trial 1 required a diastolic blood pressure above 95 mm Hg at the end of the 2-week placebo washout period, regardless of the level of the systolic pressure. Exclusion from the study was based on a serum creatinine value exceeding 1.5 mg/100 ml and abnormalities in the blood cell count.
Trial 2

Twelve patients (6 men and 6 women with a mean [± SD] age of 50.3 ± 10 years) with diastolic blood pressure above 95 mm Hg despite continuous treat-
ment with chlorthalidone 25 mg daily in the previous 4 weeks (all patients with essential arterial hypertension WHO Stage I or II) were admitted to Trial 2. After admission, they were randomized to receive captopril in two different dosing schedules: 25 mg b.i.d., and 25 mg t.i.d., in addition to continuing their unchanged diuretic therapy. The two dosing schedules were given according to a randomized within-patient open design over a 2-week period, with no interval between the two periods. The same exclusion criteria as in the Trial 1 were adopted.

In both trials, blood pressure was taken by means of a conventional mercury sphygmomanometer. The lowest values from at least three consecutive readings over a 2- to 3-minute period were registered. Systolic blood pressure was taken at the appearance of the brachial artery sounds, and diastolic blood pressure at the disappearance of the sounds (Korotkoff Phase V). This report presents only the supine values of blood pressure and heart rate, recorded after at least 10 minutes of supine rest in a quiet room. The heart rate was taken by an electrocardiographic strip, and the values were averaged from at least six consecutive R-R intervals.

Randomization in both trials was performed by a random number list only after admission of the single patient to the study. In Trial 1, three patients were not randomized because of diastolic blood pressure values lower than 95 mm Hg at the end of placebo period. In Trial 2, the 12 patients admitted represented 40% of the 30 essential hypertensive patients with diastolic blood pressure values in the range 95–110 mm Hg who had started a chlorthalidone 25 mg daily monotherapy trial.

To compare the b.i.d. and t.i.d. dosing schedules we asked the patients to come for their outpatient visit 11.30 to 12 hours after the last drug’s intake in the b.i.d. regimen, so that we could record their blood pressure and heart rate, and 7.30 to 8 hours after the last drug’s intake in the t.i.d. regimen. Blood pressure and heart rate measurements were always performed by a physician of our group (M.B.) who was not otherwise involved in the study and was unaware of the treatment schedules. Clinical visits were scheduled in the last day of each treatment period in both trials.

Statistical analysis was done using a Hewlett-Packard 41 CV programmable calculator. Analysis of variance (dosing schedule and treatment period regardless of the schedule were the known sources of variability), and Student’s t test for paired data (values of each dosing schedule vs prerandomization values) were used; p values less than 0.05 were considered significant.

Results

Results are summarized in table 1. In Trial 1, blood pressure and heart rate were not dissimilar on the four captopril regimens given as monotherapy. There was also no difference among the four treatment periods, indicating the lack of spontaneous blood pressure changes over time. Systolic and diastolic blood pressure values were lower with each captopril regimen compared to values recorded in the last day of placebo administration (all p < 0.01), while heart rate remained unchanged during captopril administration, regardless of the regimen.

In Trial 2, there was no statistical or clinical difference in blood pressure and heart rate values between the two different captopril regimens given in combination with chlorthalidone. On either regimen, systolic and diastolic blood pressure levels decreased compared to those with chlorthalidone alone (all p < 0.01), while heart rate remained unchanged. Blood pressure and heart rate did not change from the first to the second randomized period regardless of the treatment.

None of the patients complained of unwanted effects, and there were no dropouts from the study. On the basis of the count of the residual tablets on each visit, patient compliance with treatment approximated 100% on each captopril regimen tested in this study.

Discussion

In this study, captopril proved to be effective in reducing blood pressure, even at relatively low daily doses, not exceeding 150 mg per day. As suggested by Case et al.,10 it may be that a general unselected population of patients with mild or moderate hypertension may be sensitive to lower doses of captopril than those reported in literature with more severe or drug refractory forms of hypertension.10-12 Nevertheless, it seems

<table>
<thead>
<tr>
<th>Trial</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>167.5 ± 4.5</td>
<td>112.5 ± 5.8</td>
<td>72.5 ± 8.2</td>
</tr>
<tr>
<td>C 25 mg t.i.d.</td>
<td>152.9 ± 10.1*</td>
<td>100.4 ± 10.8*</td>
<td>73.5 ± 7.1</td>
</tr>
<tr>
<td>C 25 mg b.i.d.</td>
<td>155.4 ± 8.4*</td>
<td>100.8 ± 9.2*</td>
<td>73.5 ± 8.7</td>
</tr>
<tr>
<td>C 50 mg t.i.d.</td>
<td>147.9 ± 14.2*</td>
<td>95.0 ± 11.9*</td>
<td>74.0 ± 8.4</td>
</tr>
<tr>
<td>C 50 mg b.i.d.</td>
<td>149.2 ± 10.8*</td>
<td>96.7 ± 8.6*</td>
<td>73.0 ± 7.3</td>
</tr>
<tr>
<td>Trial 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ch 25 mg o.d.</td>
<td>163.7 ± 9.5</td>
<td>102.5 ± 6.0</td>
<td>73.2 ± 4.9</td>
</tr>
<tr>
<td>Ch 25 mg o.d. +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 25 mg t.i.d.</td>
<td>148.7 ± 8.3†</td>
<td>86.2 ± 10.9†</td>
<td>73.7 ± 6.3</td>
</tr>
<tr>
<td>Ch 25 mg o.d. +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 25 mg b.i.d.</td>
<td>150.0 ± 8.9*</td>
<td>87.5 ± 8.0†</td>
<td>73.5 ± 4.6</td>
</tr>
</tbody>
</table>

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; C = captopril; Ch = chlorthalidone; o.d. = once daily; b.i.d. = twice daily; t.i.d. = three times daily. Data expressed as means ± SD.

*p < 0.01 vs corresponding placebo values.
†p < 0.01 vs corresponding Ch values.
premature to draw conclusions about a possible improvement in the tolerability of captopril as a consequence of these low daily doses. In fact, each captopril regimen in this study was administered for no more than 2 weeks, and further studies are needed with more prolonged treatment. In this setting, a wide-scale comparative study of captopril vs diuretics as well as vs β-blockers would be useful to properly assess the place of converting-enzyme inhibition in the treatment of patients with mild or moderate hypertension.

Our patients showed blood pressure levels that were similar at 8 and 12 hours after the last captopril administration. Captopril's pharmacological half-life after oral administration in hypertensive patients does not seem to exceed 100 minutes. The prolonged action of the drug could be related to the formation of reversible storages of captopril disulfides, which would continue to release the parent molecule over time. Given usually in three divided doses, captopril proved as effective in only two divided doses, at least in patients with mild or moderate hypertension.

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Low-dose captopril therapy in mild and moderate hypertension. Randomized comparison of twice daily vs three times daily doses.
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