A fixed combination of metoprolol and chlorthalidone in hypertension

A clinical trial in general practice

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Summary

Seventy-one patients with mild-to-moderate essential hypertension completed 14 weeks' treatment with a single daily dose of a fixed combination of metoprolol tartrate 100 mg and chlorthalidone 25 mg (Logroton; Geigy). This represents 6958 patient-days of treatment.

Mean blood pressures, both supine and standing, and pulse rates were reduced to and maintained at clinically acceptable levels during the trial period. No patient prematurely discontinued treatment because of insufficient therapeutic effect. Two patients discontinued the medication for drug-related reasons. Patient compliance was excellent and the preparation was well tolerated.

The preparation was judged to be therapeutically effective in more than 80% of cases and is a valuable formulation for antihypertensive therapy.


The use of β-adrenergic receptor antagonists in the treatment of mild-to-moderate hypertension has been well established and accepted,1,2,3 as has the use of diuretics with their hypotensive action. Since the mode of action of these two groups of drugs differs, it was expected, and indeed found, that a combination of these two groups of drugs resulted in an enhanced antihypotensive effect. Such β-blocker/diuretic combinations have established their place in the therapy of hypertension,2-5 and fixed-combination formulations have been made available to simplify drug regimens, improve patient compliance and make therapy more convenient.

Metoprolol tartrate (Lopresor; Geigy) is a cardioselective β-blocking drug, which affects mainly the β1-receptors in the heart.6,7 It has been shown to lower blood pressure in most patients with mild-to-moderate hypertension.8,9 It has a plasma half-life of 3-4 hours, but, like other β-blockers, its hypotensive effect is relatively prolonged.10,11,12 Neither the plasma level nor half-life of the β-blocking agents is necessarily critical for the antihypertensive effects of these drugs.12,13,14,15 No clear relationship between the therapeutic effects of β-blockers and plasma level and/or half-life has been established.11,16

Chlorthalidone (Hygroton; Geigy) is a long-acting diuretic with a well-established history as an antihypertensive agent.

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Chlorthalidone (Hygroton; Geigy) is a long-acting diuretic with a well-established history as an antihypertensive agent.

The presence of any of the following precluded admission to the study: essential hypertension known to be resistant to β-blocking therapy, serum creatinine levels greater than 120 μmol/l, myocardial infarction within 3 months of entry to the trial, atrioventricular block, bradycardia of less than 50/min, congestive cardiac failure, bronchial asthma or any obstructive lung disease, severe liver disease or any other major concomitant disease.

In group 1, patients with diabetes mellitus being treated with hypoglycaemic agents were excluded, while in group 2 diabetics were excluded altogether. A further differentiation was that group 2 patients with serum potassium values of less than 3,5 mmol/l at the start of the study were excluded, while in group 1 the patients were admitted irrespective of the serum potassium value measured at the end of the placebo period.

Patients and methods

Two clinical trials in general practice were conducted more or less simultaneously. As there were only minor differences in the protocols and methods, both trials are discussed together. To distinguish between the two, reference will be made throughout the article to group 1 and group 2.

The population samples were co-operative outpatients of either sex, aged between 33 and 64 years, suffering from uncomplicated essential hypertension, from whom informed, written consent for the trial was obtained. The patients had a basal supine and standing diastolic blood pressure in the range of 95 - 110 mmHg in previously treated patients, or 100 - 120 mmHg in previously untreated patients. All patients went through an initial 2-week placebo period before active treatment.

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Group 1 (studied by B.F.R.M.): 35 patients fulfilled the entry criteria; of these, 2 did not complete the trial owing to adverse effects. The data of these patients have been used up to the time of discontinuation.

Group 2 (studied by L.I.R. and U.G.): 42 patients fulfilled the entry criteria; of these, 4 did not complete the trial, 3 because of non-drug-related factors and 1 because of protocol violation during the study. Their data have been included up to the time of discontinuation.

The pertinent demographic features of both groups are presented in Table I. Of interest is that in group 1 the White race predominated, while in group 2 Coloured and Asian patients were in the majority.

In group 1, 60% of patients had received antihypertensive medication previously, while in group 2 the figure was 83%. Previous regimens are detailed in Table II.
**TABLE I. DEMOGRAPHIC CHARACTERISTICS OF PATIENTS AT ENTRY TO TRIAL**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD)</td>
<td>Range</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>48.7 ± 1.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.5 ± 1.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.1 ± 2.1</td>
</tr>
<tr>
<td>Duration of hypertension (mo.)</td>
<td>83.4 ± 10.3</td>
</tr>
<tr>
<td>Serum creatinine† (mmol/l)</td>
<td>84.9 ± 2.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>32</td>
</tr>
<tr>
<td>Coloured</td>
<td>3</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
</tr>
</tbody>
</table>

| No. of patients evaluated | 35 | 42 |

* † 1 unknown in group 1 and 2 unknown in group 2.

**TABLE II. PATIENTS ON ANTIHYPERTENSIVE MEDICATION BEFORE ENTRY TO TRIAL**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients evaluated</td>
<td>35</td>
</tr>
<tr>
<td>On medication</td>
<td>21 (60.0%)</td>
</tr>
<tr>
<td>Not on medication</td>
<td>14 (40.0%)</td>
</tr>
<tr>
<td>Type of medication</td>
<td></td>
</tr>
<tr>
<td>B-blockers</td>
<td>13</td>
</tr>
<tr>
<td>B-blocker/diuretic</td>
<td>0</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7</td>
</tr>
<tr>
<td>Diuretic combinations</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
</tbody>
</table>

**Results**

**Blood pressure and pulse rate**

**Group 1:** Minimal fluctuation occurred in the mean pulse rate and blood pressure measurements during the placebo period. Mean pulse rates decreased throughout the active treatment period. The decrease in the mean standing pulse rate was statistically significant after 2 weeks of active treatment, while the decrease in the mean supine pulse rate was statistically significant after 6 weeks of active treatment. All mean blood pressure readings had decreased after 2 weeks of active treatment and continued to decrease throughout the active treatment period. These reductions were statistically significant. After 14 weeks of active treatment, 93.9% of patients had their supine diastolic pressures reduced to 90 mmHg or less and 78.8% had their standing diastolic pressures reduced to 90 mmHg or less.

**Group 2:** Minimal fluctuations in mean pulse rate and blood pressure measurements were noted during the placebo period. Throughout the active treatment phase, the mean pulse rate and blood pressures were statistically significantly lower than those excluded, hospitalization likely to interfere with assessment of trial medication, and for any other ethical or medical reason.
measured during the placebo period. After 14 weeks of active treatment supine diastolic blood pressure was reduced to 90 mmHg or less in 86.8% of the patients and a reduction in the standing diastolic blood pressure was observed in 84.2%. Tables III and IV show details of blood pressure and pulse rate for each group at each period during the study.

Body weight

Body weight remained stable for both groups during the study except for 1 patient in group 2. This was a woman in whom oedema caused a 4 kg rise in weight during the placebo period. As a result her placebo period was reduced and she was started on active treatment a week early. Her weight at the end of the study was 70 kg compared with 71 kg at the end of her placebo period.

Ophthalmological changes

Group 1: The optic fundi of 19 patients were normal before treatment while 16 had grade I changes. At the end of the study 3 patients showed improvement from grade I to normal, while there were no changes in the remainder of patients who completed the study.

Tolerability

Emergent effects were recorded at each visit and categorized according to a check-list. In group 1 the investigator went through the check-list with each patient individually and marked the side-effects experienced. In group 2 the approach was different: here the patients were only asked if they had experienced any noteworthy symptoms or signs at each visit during treatment. These spontaneously elicited apparent effects were then marked on the check-list by the investigators.

Group 1: During active treatment the most common effects deemed to be drug-related by the patients were: confusion/giddiness 7, tiredness 4, polyuria 4, and muscle cramp 4. In 1 patient with maturity-onset diabetes controlled by diet a deterioration in the diabetic condition was noted. This necessitated control with a hypoglycaemic agent and the patient dropped out of the study. A second patient experienced mild depression, insomnia, confusion/giddiness, thirst, headache and constipation. This patient also dropped out of the study.

Group 2: The most common drug-related adverse effect that emerged was tiredness (in 4 patients). Gastro-intestinal side-effects occurred in 4 patients (2 indigestion/heartburn, 2 diarrhoea) and 2 experienced muscle cramps.

Tolerability was considered to be good and no patient had to withdraw prematurely from the trial because of drug-related side-effects.
Compliance

According to tablet counts at each visit, compliance was excellent. In group 1 all patients were more than 90% compliant. In group 2, only 2 patients were less than 90% compliant, but neither of these was less than 88% compliant. The investigators in both groups were highly satisfied with compliance and ascribed this to the doctor/patient relationship in private practice.

Serum potassium values

The serum potassium values for both groups appear in Table V. In group 1, serum potassium values remained unchanged in 54.5% of patients after 14 weeks of treatment. In 12.1% of the remainder of the patients potassium values increased from below 3.9 mmol/l to above this value, while in 33.3% they decreased to below 3.9 mmol/l. The lowest serum potassium value recorded was in 1 patient whose value was 2.9 mmol/l after 14 weeks of treatment compared with 4.2 mmol/l after 2 weeks on placebo. Overall, the decrease in the mean serum potassium values was only statistically significant after 10 weeks of treatment.

In group 2, serum potassium values remained unchanged in 63.2% of the patients after 14 weeks of treatment. In 7.9% of the remaining patients the potassium values increased from below 3.9 mmol/l to above this value, while in 28.9% they decreased to below 3.9 mmol/l. The lowest serum potassium value recorded was 2.9 mmol/l in 1 patient after 10 weeks of treatment compared with 3.7 mmol/l at the start of trial and 4.6 mmol/l after 2 weeks on placebo. Overall, the fluctuation in the mean serum potassium value was not statistically significant in this group.

In group 1, 10 patients received potassium supplements in the form of 600 mg potassium chloride (Slow-K) tablets at some stage during the trial. Only 2 patients in group 2 received supplementary potassium. The decision to prescribe potassium supplementation was left entirely to the discretion of the investigators, who in turn took the patient’s overall clinical and laboratory picture into consideration before deciding.

Discussion

It is of interest to note the differences between the two patient groups (resulting from two more or less simultaneous clinical trials in three general practices in the same geographical area). Demographically, group 1 consisted mostly of White (91%) patients, while group 2 was made up mainly by Coloured (52%) and Asian (43%) patients (see Table I). Before the trial, only 60% of the patients in group 1, but 83% of those in group 2 had been receiving antihypertensive therapy, mainly in the form of &-blockers in group 1, and of diuretics and diuretic combinations in group 2 (see Table II).

As regards entry criteria, patients suffering from diabetes mellitus were excluded altogether from group 2, while only diabetics treated with hypoglycaemic agents were excluded from group 1. Another important difference was that patients in group 1 were admitted irrespective of their serum potassium value at the end of the placebo period, while patients with a serum potassium value of less than 3.5 mmol/l in group 2 were excluded. In the latter group only 2 patients required supplementary potassium tablets, while in group 1, 10 patients required potassium supplementation.

Side-effects were also reported differently for the two groups. The same standard check-list was used in both instances: In group 1 the investigator checked this list with each individual patient at each visit and noted the presenting effects. Patients in group 2 were only asked about side-effects, and if they answered in the affirmative, were asked to describe them. These spontaneously elicited side-effects were then noted on the check-list.

In both groups combined, 71 patients completed 14 weeks’ treatment; this represents 6958 patient-days of treatment.

Six patients discontinued treatment prematurely: 2 for drug-related reasons, 3 because of non-compliance and 1 patient who developed bradycardia of less than 50/min after 2 weeks’ active treatment (actual pulse rate 49/min).

Troublesome side-effects were minimal, only 2 patients dropping out because of symptoms severe enough to warrant discontinuation. (One diabetic patient, controlled on diet only, experienced a deterioration of diabetes, and a second patient withdrew after experiencing mild depression, insomnia, confusion, thirst, headache and constipation.)

Serum potassium values declined as expected and this serves as a useful reminder that all patients should have electrolyte measurements during &-blocker/diuretic regimens. However, the importance of a decrease in serum potassium levels as well as the role of potassium supplements in such a regimen has been questioned.

We conclude that metoprolol tartrate 100 mg and chlorothalidone 25 mg in a fixed combination taken once a day is effective in controlling mild-to-moderate uncomplicated essential hypertension in general practice. It was generally well tolerated in the two clinical trials concerned.

We wish to thank Drs I. J. Eidelman and J. Malan of the Medical Department, Ciba-Geigy (Pty) Ltd, for supplying the trial material, and Miss S. Carey of the same Department for assistance with the statistical analysis.

REFERENCES