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Comparison of Metoprolol and Hydrochlorothiazide as Antihypertensive Agents

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Summary. A crossover comparison of metoprolol and hydrochlorothiazide has been performed in 20 patients with mild hypertension. Both drugs caused almost identical statistically significant reduction in blood pressure of about 20 mm Hg systolic and 15 mm Hg diastolic. The side effects during active therapy were few and mild, but 5 patients experienced subjective symptoms during the first few days following abrupt withdrawal of metoprolol, namely general malaise, palpitations, headache, sweating and tremor. The symptoms were more pronounced in the standing postition and disappeared at once on resumption of β-blocker therapy, or gradually over 5 - 7 days when placebo tablets were given. In 11 of the 20 patients hydrochlorothiazide produced subnormal serum potassium levels and potassium supplements were given. The serum uric acid level was also significantly increased during hydrochlorothiazide treatment.

Key words: Metoprolol, hydrochlorothiazide, beta-blocker withdrawal, essential hypertension.

The role of β-blocking agents in the treatment of arterial hypertension has now been clearly established. Their mode of action has still not been fully elucidated, but minor pharmacological differences between the agents, such as the degree of intrinsic sympathomimetic or local anaesthetic effects, seem to be of no significance for the reduction of blood pressure. Both selective β_1-blocking agents and non-selective β-blockers have been shown to lower the blood pressure effectively, the reduction in pressure produced by moderate doses being similar to that achieved by use of diuretics (Bengtsson, 1972a; Muckadell and Gyntelberg, 1973). Metoprolol[1] is a new selective β_1-receptor blocking agent devoid of intrinsic sympathomimetic activity (Åblad et al., 1973). In a preliminary trial it was found to be effective in lowering raised blood pressure with few side effects (Pedersen, 1975). In the present study the effect of metoprolol has been compared with that of hydrochlorothiazide, one of the most commonly used antihypertensive agents.

PATIENTS

Twenty-one patients with mild arterial hypertension (WHO I - II) agreed to participate in the trial. Patients suffering from chronic bronchitis, bronchial asthma, cardiac failure or diabetes mellitus were not accepted for it. In two a renal aetiology could not be excluded and the others had essential hypertension.

Twenty patients completed the trial, 10 women and 10 men; one patient was withdrawn during the run-in period for reasons stated under the heading "Drop-

1 Metoprolol (pINN) = H 93/26, Seloken®/Betaloc® (AB Hässle/AB Astra, Sweden)

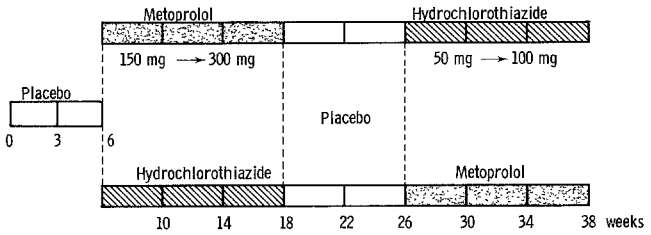

Fig. 1. Design of the trial

outs". The mean age was 44 years (range 29 - 63 y). The known duration of the hypertension exceeded three years in only three patients. Eight of the patients had not previously been treated, five had received diuretics and seven β-blockers. Control had been satisfactory in most of the patients previously treated. Four of the patients received concomitant therapy with antidepressants during the trial and one received laevothyroxin.

METHODS

The study was designed as a crossover study and the active drugs were given in a randomized order. The patients were told that they would be given different types of therapy during the trial and they did not know that some of the tablets would be placebo. The design of the study is shown in Figure 1. The patients were first observed during a 6-week placebo period and were then randomly chosen to receive metoprolol or hydrochlorothiazide as first active drug. The dose of metoprolol was 50 mg t.i.d., and that of hydrochlorothiazide was 25 mg b.d. After 4 weeks dosage was increased to 100 mg t.i.d. or 50 mg b.d., respectively, if the supine diastolic pressure was still > 95 mm Hg. This dose was then maintained for a period of 8 weeks, whilst the patients were seen every 4 weeks. The first period of active therapy was followed by an 8-week period during which the patients received 3 placebo tablets a day. After this time a new period of active therapy was undertaken with the drug that the patient had not previously received. The hydrochlorothiazide was genuine Hydrochlorothiazid® M.S.D. tablets of 25 mg. The metoprolol tablets contained 50 mg. The placebo tablets were identical in appearance to the latter and were given three times a day. The drugs were packed in bottles labelled with a code number and the number of tablets remaining was counted by the investigator after each treatment period.

At each examination blood pressure and heart rate were determined after rest in the supine position for 5 - 10 minutes and after standing for 1 minute. All blood pressures were recorded by the investigator using the same sphygmomanometer. The blood pressure was measured in the right arm and the diastolic pressure was read at phase V. Haemoglobin, haematocrit, white blood count, serum creatinine, serum potassium, serum sodium, serum chloride and serum uric acid were checked regularly throughout the study. ECG was recorded and the patient's body weight was noted. If serum potassium fell to ≤3.5 mmol/l, potassium supplementation with KCl 750 mg t.i.d. was given.

STATISTICAL METHODS

The significance of change in blood pressure and heart rate was calculated by analysis of variance followed by Scheffe's contrast. Student's t-test was used for body weight and laboratory data. All tests were done two-tailed and statistical significance was taken as $p < 0.05$.

RESULTS

Blood Pressure and Heart Rate

The means of the blood pressures and heart rates during the trial are shown in Table 1, and Figure 2 illustrates the blood pressure changes in the two groups; the initial blood pressure in the groups was similar. It will be seen that the washout period between treatment was sufficiently long to give pretreatment levels of diastolic pressure and only a minor reduction in the mean systolic pressure. All patients had a diastolic blood pressure of ≥ 100 mm Hg at the end of this period.

The average reduction of blood pressure amounted to 25/17 mm Hg ($p < 0.001$) and 33/14 mm Hg ($p < 0.001$) in the supine position after 12 weeks' treatment with metoprolol and hydrochlorothiazide, respectively. The corresponding reduction of blood pressure in the standing position was 23/18 mm Hg ($p < 0.001$) and 33/17 mm Hg ($p < 0.001$) after metoprolol and hydrochlorothiazide, respectively. There was no significant difference between the two drugs in this respect. Heart rate was significantly reduced during metoprolol treatment by about 20 beats/min in the supine and standing positions, but did not change significantly during the hydrochlorothiazide period.

Table 1. Mean values for blood pressure, heart rate and weight during the trial, (Mean± SEM), (n = 20)

		At end of run-in period	Metoprolol 4 weeks	Metoprolol 12 weeks	At end of wash-out period	Hydrochlorothiazide 4 weeks	Hydrochlorothiazide 12 weeks
Supine BP (mm Hg)	Systolic	177 ± 4.2	155 ± 6.9	152 ± 6.3	169 ± 3.9	152 ± 3.7	144 ± 3.7
	Diastolic	111 ± 1.7	96 ± 2.5	94 ± 2.8	109 ± 1.7	101 ± 2.3	97 ± 2.2
Standing BP (mm Hg)	Systolic	170 ± 3.5	148 ± 5.8	147 ± 5.6	162 ± 4.1	146 ± 3.7	137 ± 3.3
	Diastolic	119 ± 1.5	101 ± 2.3	101 ± 2.5	115 ± 2.5	108 ± 2.2	102 ± 2.3
Heart rate (beats/min)	Supine	83 ± 2.5	64 ± 1.9	65 ± 2.4	82 ± 2.8	87 ± 3.2	83 ± 2.7
	Standing	89 ± 3.1	70 ± 1.8	69 ± 2.5	91 ± 2.8	99 ± 2.5	94 ± 2.9

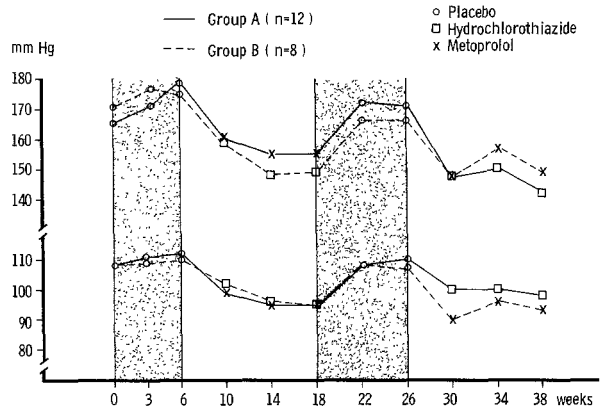

Fig. 2. The supine blood pressure (mean) during the trial in patients who started on metoprolol (Group A) and those who started on hydrochlorothiazide (Group B)

Table 2. Mean values for body weight and laboratory values during the trial (Mean ± SEM) (n = 20)

	Run-in	Metoprolol	Hydrochlorothiazide
Body weight (kg)	72.7 ± 2.7	73.0 ± 2.5	71.9 ± 2.6
Potassium (mmol/l)	4.2 ± 0.1	4.3 ± 0.1	3.6 ± 0.1
Uric acid (mmol/l)	0.30 ± 0.02	0.33 ± 0.03	0.37 ± 0.03

In 9 patients the dose of metoprolol was increased to 300 mg daily, whereas 15 required an increase of the dose of hydrochlorothiazide to 100 mg daily.

Body Weight, Serum Potassium and Uric Acid

The mean values ± SEM are shown in Table 2. The average body weight was 1 kg lower during the hydrochlorothiazide period compared to the metoprolol and placebo periods ($p < 0.05$). Serum potassium was significantly lower during the hydrochlorothiazide period than during the other periods, even though potassium substitution had been given to 11 patients ($p < 0.01$); the mean reduction amounted to 0.6 mEq/l compared to placebo. There was also a significant rise in serum uric acid of 0.07 mmol/l during the hydrochlorothiazide period ($p < 0.01$). The changes in serum potassium and uric acid after hydrochlorothiazide were not considered to be of any clinical significance.

Side Effects

In general, the reported side effects were few and mild during the periods of active treatment. In the metoprolol period one patient had cold extremities and another complained of shortness of breath. Whilst on hydrochlorothiazide two patients felt depressed, one had palpitations, and one complained of tiredness.

The most surprising feature was the subjective symptoms experienced by some patients after abrupt withdrawal of metoprolol. One patient was unable to complete the run-in period due to reasons given below under the heading "Drop-out". In another four patients subjective symptoms, such as general malaise, palpitations and headache, occurred during the first few days after withdrawal of metoprolol. One of these patients suffered from depressive neurosis and was receiving imipramine. Another patient had had an thyroidectomy

and was treated with laevothyroxine; she was considered to be in an euthyroid state.

One patient was hospitalized after four weeks on placebo for a suspected myocardial infarction, which was not verified.

Drop-Out

One patient, previously treated with metoprolol, was unable to complete the run-in period on placebo, as about 24 hours after cessation of the metoprolol therapy he began to feel uncomfortable and developed general malaise, headache, sweating and palpitations. These effects lasted for two days and forced him to take to his bed, as the symptoms were less pronounced in the supine position. His resting pulse was 112 beats/min on the third day. The symptoms disappeared within 1 - 2 hours after resumption of metoprolol therapy.

Acceptance of Treatment

On counting the remaining tablets, it was found that no patient had taken less than 75% of the prescribed dose of either drug.

DISCUSSION

The results in this study show that metoprolol and hydrochlorothiazide were equally effective in lowering blood pressure. Similar results have been reported by Muckadell and Gyntelberg (1973), who found that chlorthalidone and pindolol led to a similar reduction in blood pressure. In a double-blind trial the antihypertensive effect of chlorthalidone 50 mg daily was found to be more pronounced than that of alprenolol 400 mg daily, but when the dosage of the latter was increased almost the same decrease in blood pressure was attained (Bentsson, 1972a).

In fifteen of the 20 patients in the present trial the dose of hydrochlorothiazide was increased from 50 mg to 100 mg daily at the 4-week visit, because their diastolic blood pressure was higher than 95 mm Hg. On average this resulted in a further reduction of 8/7 mm Hg. Degnbol, Dorph and Marner (1973) also found a relatively small reduction of blood pressure on doubling the dose of hydrochlorothiazide.

A subnormal serum level of potassium was found during treatment with hydrochlorothiazide but the clinical significance of this finding is debatable (Wilkinson et al., 1975). Transient elevation of serum uric acid has been found after β-blockers (Bentsson, 1974), but in the present study an elevation was found only after hydrochlorothiazide.

Five of the present patients complained of side effects, such as general malaise, headache and palpitations, after abrupt withdrawal of metoprolol. Similar symptoms in hypertensive patients have also been described by O'Brien and McKinnon (1972) after withdrawal of propranolol. The frequency of these side effects was relatively high in the present investigation, but they have not been found in other double-blind studies following abrupt withdrawal of alprenolol (e.g. Bengtsson, 1972a and b), pindolol (Muckadell and Gyntelberg, 1973) or metoprolol (Stokkeland et al., 1975; Bengtsson, 1976; Jäättelä and Pyörälä, 1976). This may indicate that symptoms following abrupt withdrawal of β-blockers are not so frequent in hypertensive patients, but the problem they represent might be more important in angina pectoris. Thus, Alderman et al. (1974) suggested that sudden withdrawal of β-blockers in patients with angina pectoris resulted in unstable angina, or even sudden death due to myocardial infarction. Withdrawal symptoms in angina pectoris have also been revealed in a recent controlled study (Miller et al., 1975). In the present investigation the withdrawal symptoms were abolished when therapy with metoprolol was recommenced. A method for avoiding these side effects that is likely to be successful, would be to withdraw the β-blocker gradually when necessary, e.g. before a surgical operation.

The mechanism underlying the clinical effects seen in some of the patients following withdrawal of β-blockers is not known. Increased levels of circulating catecholamines, which have been found during β-blockade by Galbo et al. (personal communication), could explain the observed phenomena. However, in a later study no change in plasma catecholamines was found in six hypertensive patients during the first week after cessation of β-blockade (unpublished data). An increase in the sensitivity of the β-receptor could also account for the clinical picture.

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