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Comparison of the Antihypertensive Effect of Urapidil and Metoprolol in Hypertension

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Summary. The hypertensive effect of urapidil, a new antihypertensive agent that acts via central and peripheral alpha-adrenoceptors, has been compared with that of metoprolol in 40 patients with mild essential hypertension. Blood pressure was significantly reduced by both drugs, while the heart rate was reduced only after metoprolol. The increases in systolic blood pressure and heart rate caused by three progressive work loads of bicycle exercise were not affected during urapidil, whereas both were reduced by metoprolol. A slight reduction in forced expiratory volume was observed in some patients during treatment with the beta-blocker. There was no case of orthostatic hypotension during urapidil administration, despite its alpha$_1$-blocking action. Side-effects were rare and negligible with both drugs.

Key words: urapidil, metoprolol; antihypertensive treatment, exercise test, haemodymic effects, side-effects

Urapidil is a phenylpiperazine derivative [1] that acts upon central and peripheral alpha-adrenoceptors [2, 3] like clonidine and prazosin. Animal and human studies have shown that both acute and chronic administration of urapidil can effectively lower blood pressure [4, 5] with a low incidence of tachycardia and/or orthostatic hypotension [6], the most common side-effects that have previously limited clinical use of alpha$_1$-adrenergic blocking agents. The present double-blind crossover study is a comparison of the antihypertensive efficacy and side effect profiles of urapidil and the selective beta$_1$-blocker, metoprolol.

Material and Methods

Forty out-patients with mild to moderate essential hypertension took part in the study. There were 20 males and 20 females, aged 33 to 62 years. All patients had WHO Stage I or II hypertension.

After a 2-week period of wash-out from any previous antihypertensive treatment, during which a placebo tablet was administered b.i.d., the patients were randomly allocated to receive either urapidil 30 mg b.i.d. or metoprolol 100 mg b.i.d. for 4 weeks. Then they were again given placebo for a further 2-week wash-out period, before crossing over to the other active medication for 4 weeks.

Blood pressure and heart rate were measured after 10 min in the supine position and 3 min upright. This was done at weekly intervals in the outpatient clinic, 3-4 h after dosing. Blood pressure was measured with a mercury sphygmomanometer; the diastolic level corresponded to disappearance of the Korotkoff sounds (Phase V); heart rate was measured over 30 s at the radial pulse.

At the end of each active and placebo period bicycle exercise was performed between the 3rd and 4th h following drug administration, using progressive work loads of 25, 50 and 75 W, each step lasting 2 min. Systolic blood pressure and heart rate were recorded immediately before and at the end of each exercise step.

At the end of placebo and active drug periods, forced expiratory volume (FEV) was measured, and blood was taken for assay of plasma renin activity (after 1 h in the upright position) and for routine hematological and biochemical tests.

Spontaneously reported side-effects and those elicited by the specific questions by the doctor were recorded during the weekly visits.

Statistical analysis used Student's t-test for paired data and variance analysis. $p = 0.05$ was taken as the lowest significance level.

Results

Blood pressure and heart rate data are reported according to the sequence of urapidil and metoprolol administration and after pooling all the data.

1st Sequence Placebo-Urapidil-Placebo-Metoprolol (18 Patients)

Supine blood pressure (mean ± SEM) at the end of the placebo run-in period was 160 ± 3/103 ± 1 mmHg. It was significantly reduced to 152 ± 3/97 ± 1 mmHg ($p < 0.01$ for systolic and $p < 0.001$ for diastolic values, respectively) during urapidil treatment. At the end of the second 2-week placebo period blood pressure had returned to 165 ± 3/105 ± 2 mmHg and it subsequently fell to 149 ± 2/96 ± 1 mmHg on metoprolol ($p < 0.001$ for systolic and $p < 0.01$ for diastolic pressure).

Upright blood pressure was significantly reduced by urapidil from 156 ± 2/102 ± 1 to 145 ± 2/93 ± 1 mmHg ($p < 0.01$ for systolic and $p < 0.001$ for diastolic values). During metoprolol treatment it was also significantly ($p < 0.01$) reduced from 155 ± 2/104 ± 1 to 148 ± 3/93 ± 1 mmHg.

Heart rate did not change during the 4 weeks of urapidil treatment, whereas it was reduced ($p < 0.001$) during metoprolol therapy (from 77 ± 2 to 64 ± 1 beats/min supine, and from 83 ± 1 to 66 ± 1 beats/min, upright).

2nd Sequence Placebo-Metoprolol-Placebo-Urapidil (20 Patients)

Supine blood pressure at the end of the placebo run-in period was 158 ± 3/102 ± 2 mmHg and it was not significantly different from the levels in patients randomly allocated to the first sequence. Metoprolol significantly reduced blood pressure to 149 ± 3/96 ± 2 mmHg ($p < 0.001$ for systolic and $p < 0.01$ for diastolic blood pressure), and after urapidil it was reduced from 159 ± 3/102 ± 2 to 154 ± 3/97 ± 3 mmHg, a non-significant difference.

In the upright posture metoprolol significantly decreased blood pressure from 154 ± 2/100 ± 2 to 140 ± 3/91 ± 2 mmHg ($p < 0.01$ for systolic and $p < 0.001$ for diastolic values), and urapidil lowered it from 154 ± 3/99 ± 2 to 146 ± 3/96 ± 2 mmHg, only the reduction in systolic blood pressure being statistically significant ($p < 0.05$).

Heart rate did not change during urapidil treatment, while, as expected, it was significantly reduced by metoprolol (from 76 ± 2 to 64 ± 2 beats/min supine, and from 84 ± 3 to 66 ± 1 beats/min upright; $p < 0.001$).

Pooled Data

When the blood pressure and heart rate values in the four different placebo periods were compared, no significant difference was found with the subjects either supine or upright. Therefore, blood pressures and heart rates in the two sequences have been pooled and analyzed according to the drug administered, but independent of the sequence followed.

Supine blood pressure was significantly ($p < 0.01$) reduced from 159 ± 3/102 ± 2 to 154 ± 3/97 ± 2 mmHg after urapidil, and to 148 ± 3/95 ± 2 mmHg after metoprolol. In the upright posture blood pressure was significantly reduced ($p < 0.01$) to 146 ± 3/94 ± 1 mmHg after urapidil, and after metoprolol to 142 ± 3/92 ± 1 mmHg, as compared to the placebo values of 154 ± 3/102 ± 2 mmHg. Supine diastolic blood pressures of 95 mmHg or less were observed in 17 patients on urapidil and in 15 on metoprolol.

The supine heart rate after placebo, urapidil and metoprolol was 77 ± 2, 78 ± 1 and 64 ± 1 beats/min, respectively; in the upright position it was 82 ± 2 after placebo, 85 ± 2 after urapidil and 64 ± 1 beats/min after metoprolol. Only the heart rate after metoprolol was significantly ($p < 0.001$) reduced, when compared both to placebo and urapidil treatment. Supine heart rates higher than 90 beats/min were observed only in 3 patients on urapidil, and lower than 50 beats/min in only 1 patient on metoprolol.

Exercise Test

The exercise induced changes in systolic blood pressure and heart rate in the placebo periods were comparable so the values have been pooled. During urapidil administration the exercise-induced increments in systolic blood pressure were not changed significantly (Fig. 1) when the results were considered together. The sole exception was the rise at the 50 Watt load in the 2nd sequence, which was significantly ($p < 0.05$) reduced. Metoprolol significantly reduced the rise in systolic blood pressure at all loads, independent of the sequence and of pooling of the results.

The exercise-induced changes in heart rate (Fig. 1) were not modified by urapidil. During metoprolol there was a statistically significant reduction in the heart rate increment ranging from −18 to −27

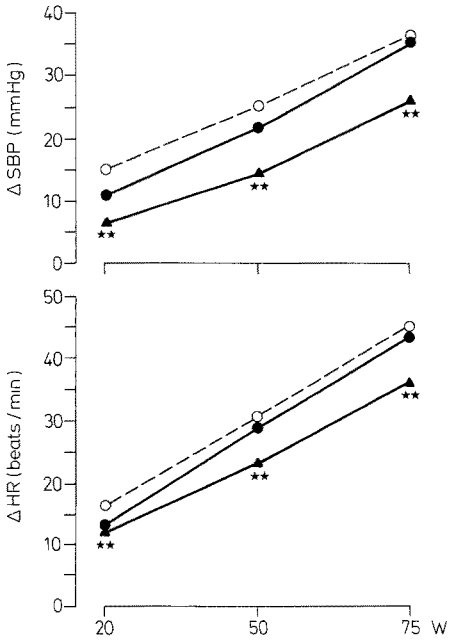

Fig. 1. Exercise-induced increases in systolic blood pressure (Δ SBP) and heart rate (Δ HR) during placebo, urapidil and metoprolol treatment of hypertensive patients. O-----O placebo; ●—● urapidil; ▲—▲ metoprolol; $^{**}p < 0.01$ Vs placebo

beats/min ($p < 0.01$ to $p < 0.001$), independent of the analysis followed (sequence or pooling of data).

Pulmonary Function

Urapidil did not cause a change in pulmonary function assessed as FEV (before drug 2.93 l/s, after 2.97 l/s). Metoprolol led to a mild, but significant ($p < 0.01$) reduction from 2.91 to 2.75 l/s but only in the 2nd sequence of drug administration.

Plasma Renin Activity

Only metoprolol significantly ($p < 0.001$) reduced plasma renin activity in the upright position of hypertensive patients (from 0.81 ± 0.12 to 0.44 ± 0.09 ng Ang I/ml/h), as there was no change after urapidil (from 0.76 ± 0.14 to 0.85 ± 0.16 ng Ang I/ml/h).

Side-Effects

There were 2 drop-outs from the study: one patient discontinued treatment with urapidil because of nausea during the 1st sequence, and the other was withdrawn for headache during placebo treatment also in the 1st sequence. During urapidil treatment 4 patients complained of dizziness, 2 of fatigue, 2 of nausea and 1 of lightheadness, while in the metoprolol period 2 patients complained of dizziness and 2 patients of fatigue.

Discussion

In the present study a comparison has been made of the clinical efficacy and tolerability of urapidil versus metoprolol, a selective $beta_1$-adrenoceptor blocking agent, in 40 patients with mild essential hypertension, according to a double-blind, cross-over, randomized study. A betablocker was selected as the reference drug because of the wide clinical experience of beta-blockers in the treatment of hypertension, and as both drugs act on the sympathetic nervous system. Urapidil (30 mg b.i.d.) and metoprolol (100 mg b.i.d.) both caused a similar and significant reduction in blood pressure in the patients in the first sequence, when urapidil was given first and metoprolol second. Urapidil was slightly less effective than metoprolol in the patients in the second sequence, when metoprolol was given first, followed by urapidil second. However, patients who received the second sequence had a slightly lower blood pressure than those in the first sequence, and the smaller overall response to urapidil was due to 6 patients who did not respond at all. In any case, when the data for the two sequences were pooled, both urapidil and metoprolol caused statistically significant lowering of systolic and diastolic blood pressure. The heart rate was unmodified after urapidil. As expected, it was significantly decreased during metoprolol administration, without reaching values below 50 beats/min.

If the results are compared with those of Schoetensack et al. [5], it appears that the blood pressure reduction here was undoubtedly smaller. However, in the previous study the dose of urapidil was increased to 30 mg t.i.d. whenever necessary, and the average pre-treatment blood pressure was higher.

Although urapidil, like prazosin, has $alpha_1$-adrenoceptor blocking activity, in the present patients it lowered blood pressure in the lying and upright positions to a similar extent, and no case of orthostatic hypotension was observed. On the whole urapidil did not cause significant side effects in these hypertensive patients; only one patient dropped out while receiving urapidil, and the side effect he presented (nausea) was not considered to be related to treatment. Another drop-out occurred during placebo. Other mild adverse reactions reported during urapidil treatment were dizziness, nausea and lightheadness. During metoprolol treatment patients complained of dizziness and fatigue. Some of these side effects occur whenever blood pressure is reduced, regardless of the drug employed, although dizziness may be more frequent when the reduction is greater in the upright than in the supine posture.

In conclusion, our clinical experience of urapidil

indicates the absence of episodes of orthostatic hypotension and/or tachycardia despite its alpha$_1$-blocking action. It is possible that central alpha$_2$-adrenoceptor activation, a property also described for urapidil [3], can counterbalance the reflex activation of the sympathetic nervous system secondary to the decrease in peripheral vascular resistance. Maintenance of postural and exercise blood pressure regulation during urapidil administration may result from its predominant effect on resistance vessels, with no clinically significant action on capacitance vessels.

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