Clinical Aspects of Antihypertensive Therapy with Urapidil
Comparison with Hydrochlorothiazide

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Summary

To define the efficacy and tolerability of urapidil as a monotherapy in ambulatory patients with hypertension, we compared urapidil with a standard first-line antihypertensive agent, hydrochlorothiazide (HCT), in a multicentre general practice trial.

The study was an 8-week double-blind randomised parallel-group comparison, with a 3-week pretreatment phase (1 week of gradual reduction of antihypertensive agents, 2 weeks of placebo). Blood pressure and heart rate were monitored using an automatic device (boso-digital S II), in the morning after the last intake of medication in the evening before. The dosages of urapidil used were 30mg, 60mg or 90mg twice daily; the dosages of HCT were 12.5mg/day or 12.5 or 25mg twice daily. If necessary, dosage adjustments were performed every 2 weeks.

Data from 165 patients could be evaluated (urapidil, n = 78; HCT, n = 87). Sitting blood pressure was reduced significantly, by 9.4/7.1mm Hg with urapidil and by 20.7/11.2mm Hg by HCT. The effect of HCT on systolic (p < 0.001) and diastolic (p < 0.05) blood pressure was significantly more pronounced than that of urapidil. The response rates (diastolic blood pressure decreased to ≤ 90mm Hg or by ≥ 10mm Hg) were 36% of patients with urapidil and 56% with HCT. Heart rate was not significantly affected by either treatment.

Although serum potassium was significantly decreased (from 4.4 to 4.0 mmol/L) and low density lipoprotein (LDL)-cholesterol as well as uric acid were significantly increased (from 142 to 153 mg/dl and from 4.8 to 5.7 mg/dl, respectively) with HCT treatment, no significant changes were observed with urapidil.

Urapidil was generally well tolerated and did not cause adverse metabolic effects, which might counterbalance the beneficial effects of blood pressure reduction.

The antihypertensive action of urapidil has been shown to be due to a peripheral α1-adrenoceptor blocking action as well as to central serotonin1A-receptor agonist activity (van Zwieten 1989). Compared with other α1-adrenoceptor blocking substances, urapidil does not appear to exert a 'first-dose' phenomenon, reflex tachycardia or sodium retention during long term therapy.

Comparative studies have shown that urapidil at dosages between 30 and 120 mg/day is as effective in lowering blood pressure in patients with mild to moderate essential hypertension as many other
antihypertensive agents: acebutolol (Tzincoca et al. 1985), metoprolol (Leonetti et al. 1989), atenolol (Török et al. 1988), metipranolol plus butizide (Schäfer 1982), captopril (Rosenthal & Haerlin 1989), prazosin (Kaneko et al. 1988) or nitrendipine (Winn 1988). In 2 studies, however, the decrease in systolic blood pressure after treatment with urapidil was less pronounced than that after therapy with α-methyldopa (Feldstein et al. 1988) or slow release nifedipine (Stumpe et al. 1989).

So far, no comparative study has been performed with the standard antihypertensive agent, hydrochlorothiazide (HCT). We therefore conducted a general practice multicentre trial to define the efficacy and tolerability of urapidil as a monotherapy in comparison with HCT. Since cardiovascular risk is not determined by elevated blood pressure only but also by other risk factors such as high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, blood glucose (Kannel 1987) and perhaps serum potassium (Kaplan 1984), these parameters were examined as well.

1. Patients and Methods

The objective of the study was to determine the number of patients in whom sitting diastolic blood pressure was reduced to ≤ 90 mm Hg or by at least 10 mm Hg after 8 weeks of monotherapy with either urapidil or HCT.

Patients were included in the study only after giving their informed consent. The study protocol was approved by the Freiburg Ethics Committee.

1.1 Study Design

The design was a multicentre randomised double-blind controlled trial involving 25 study sites (predominantly general practices), with a single-blind 2-week placebo run-in period. The placebo phase was preceded by a 1-week washout period for patients who had been previously treated with antihypertensive drugs. Only those patients demonstrated to have essential hypertension, defined as a diastolic blood pressure (mean of 5 consecutive measurements in sitting position) between 95 and 120 mm Hg at the end of the placebo run-in phase proceeded to active treatment.

At visit 4 i.e. week 0, the patients were randomly allocated to active treatment with either urapidil 30 mg twice daily or HCT 12.5 mg in the morning and placebo in the evening in identical capsules. 132 patients (68 female) were randomised to treatment with urapidil and 127 patients (65 female) with HCT. During the 8-week double-blind treatment period, the patients were seen every 2 weeks at which time dosage was adjusted in patients with an inadequate response. The urapidil dose could be increased to either 60 or 90 mg, twice daily and the HCT dose to either 12.5 or 25 mg twice daily.

1.2 Exclusion Criteria

Exclusion criteria were as follows: antihypertensive therapy which could not be stopped; long term treatment of other diseases with β-blockers, diuretics or calcium antagonists; congestive heart failure (New York Heart Association grades III or IV); sick sinus syndrome; second or third degree atrioventricular heart block; bradycardia (heart rate < 50 beats/min); myocardial infarction within the last 6 months; ≥ 30% overweight (Broca-Index); malignant disease; psychosis; severe infection; severe renal or liver disease; stroke; pregnancy or use of oral contraceptives; serum creatinine > 150 μmol/L; serum potassium < 3.6 mmol/L; age < 25 or > 69 years.

1.3 Measurement of Blood Pressure and Pulse Rate

Blood pressure was measured on 3 separate occasions before active treatment was started to avoid a spontaneous decline in blood pressure, as was observed, for instance, during placebo treatment in the Australian Therapeutic Trial (Management Committee of the Australian Therapeutic Trial in Mild Hypertension 1982). To ensure standardised blood pressure recordings in all centres, blood pressure was measured by means of an automatic de-