Eur J Clin Pharmacol (1985) 28: 35–39

European Journal of Clinical Pharmacology

Antihypertensive Effects of Urapidil and Clonidine: A Double-Blind Cross-Over Study

E. Kanniainen[2], O. Heikkilä[2], T. Jääskeläinen[2], M. Lilja[1], and A. J. Jounela[1]

[1]Department of Medicine, University of Oulu, Oulu and [2]Department of Medicine, Kemi Central Hospital, Kemi, Finland

Summary. The antihypertensive effects of urapidil and clonidine have been studied in a double-blind cross-over trial in 11 hypertensive outpatients with mild to moderate hypertension, at rest and during isometric exercise. Urapidil 30 mg b.i.d. significantly decreased the standing diastolic blood pressure ($p < 0.05$) and the systolic blood pressure at the end of isometric exercise ($p < 0.05$). Clonidine 0.075–0.15 mg b.i.d. was more effective in decreasing both systolic and diastolic blood pressure in the supine and standing positions as well as during isometric work ($p < 0.05$–0.001). Urapidil caused fewer side-effects than clonidine. Overall, in the doses used urapidil had a weaker antihypertensive effect and caused fewer side-effects than clonidine.

Key words: urapidil, clonidine, hypertension; side-effects, hypotensive effect

Urapidil, 6-(3-(4-(O-methoxyphenyl)-1-piperazinyl)-propylamine)-1,3-dimethyluracil (Fig. 1), is a new compound, which has been shown to produce antihypertensive effects both in experimental animals and man [1,2]. The mode of action of urapidil appears to involve stimulation both of central alpha-adrenoceptors and peripheral presynaptic alpha-adrenoceptors, as well as blockade of peripheral post-synaptic alpha-adrenoceptors [3]. Thus, part of its antihypertensive effect may be due to a mechanism similar to that considered to mediate the antihypertensive effect of clonidine. With this in mind a study has been made of the antihypertensive effects of urapidil and clonidine in a double-blind cross-over trial in out-patients with mild or moderate hypertension.

Materials and Methods

Patients

Initially, 12 out-patients, 4 male and 8 female, aged 31–58 years, weighing 52 to 85 kg, entered the study. One man dropped out due to poor co-operation. The hypertension was graded as WHO I in 6 and WHO II in 5 patients. Nine out of 11 patients had not had previous antihypertensive therapy, and in 2 patients atenol 100 mg once daily was stopped four weeks before the study.

Trial Design and Protocol

The trial design is shown in Fig. 2. During the 6 week run-in period the patients received placebo at 8 a.m. and 8 p.m. Then they were allocated to 2 groups according to a randomization schedule. Five patients (Group I) started with urapidil 30 mg at 8 a.m. and placebo at 8 p.m. and 6 patients (Group II) with clonidine 0.075 mg at 8 a.m. and 0.075 mg at 8 p.m. The patients received the drugs in capsules which were identical in appearance and taste. After the first two-week dose-titration period the dose of urapidil was increased to 30 mg at 8 a.m. and 30 mg at 8 p.m., and the dose of clonidine to 0.15 mg at 8 a.m. and 8 p.m., unless the supine diastolic blood pressure fell below 95 mmHg or intolerable side-effects occurred.

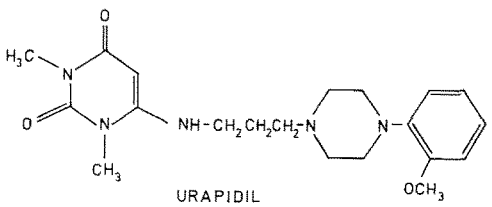

Fig. 1. Urapidil

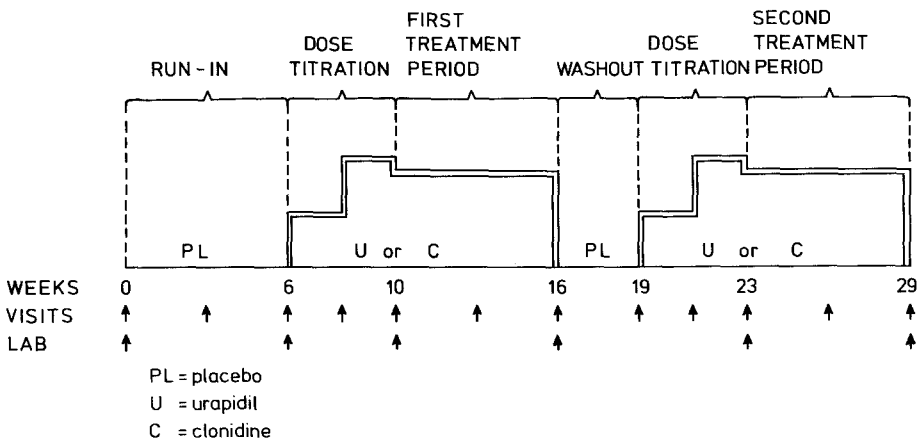

Fig. 2. Design of the study

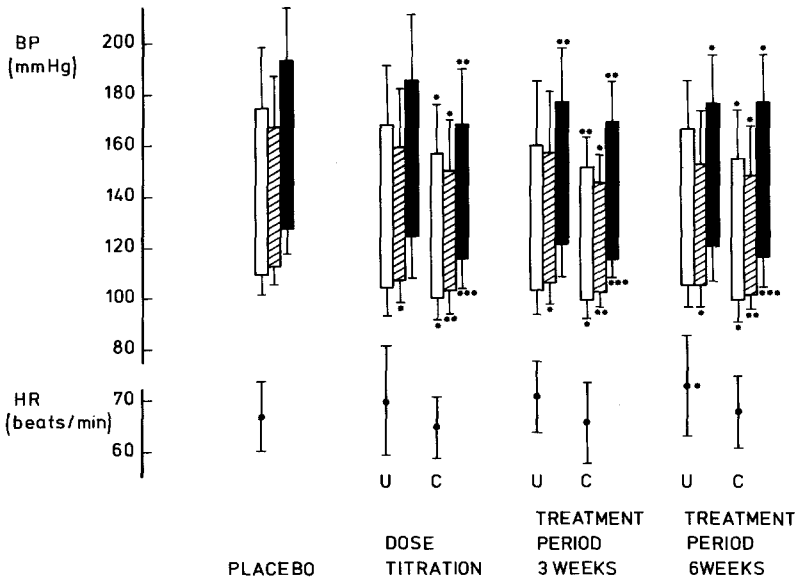

Fig. 3. Systolic and diastolic blood pressure and heart rate (mean ± SD) in the supine and standing positions, and at the end of isometric work, at the end of placebo period and after the dose titration and 3 and 6 week treatment periods in 11 patients. U = urapidil; C = clonidine; * $= p < 0.05$, ** $= p < 0.01$, *** $= p < 0.001$ compared to placebo period; □•supine; ▨ standing; ■ isometric; $n = 11$

The dose of urapidil thus titrated was 30 mg in 1 patient and 30 mg b.i.d. in 10 patients. The corresponding doses of clonidine were 0.075 b.i.d. in 5 patients and 0.15 mg b.i.d. in 6 patients. The second treatment period lasted 2 weeks and was followed by the double-blind cross-over phase of the study, which consisted of two 6 week treatment periods separated by a 3 week wash-out period during which placebo capsules were administered twice daily. The change from active drug treatment to placebo treatment was carried out abruptly in view of the low doses of clonidine. Blood pressure was measured 24 h after abrupt cessation of active drug treatment and no evidence of rebound hypertension was found. Patients were asked to contact the nurse in case of any new subjective symptoms after cessation of active drug treatment, but no patient did so. Patients in Group I were treated during the first 6 week treatment phase with urapidil and during the second 6 week treatment phase with clonidine, the dose of which was again titrated. Patients in Group II started with clonidine and after the wash-out period received urapidil, the dose of which was titrated.

Procedures

On the first visit, after taking the medical history, a physical examination, chest X-ray and electrocardiogram were done and blood and urine specimens were obtained for the following laboratory determinations: blood count, erythrocyte sedimentation rate, serum sodium, potassium, calcium, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and uric acid. These examinations were repeated after the first and second dose-titration periods, as well as after the two treatment periods.

Blood pressure throughout the study was measured in the same room of the out-patient clinic, by the same trained nurse using the same standard

Table 1. Systolic and diastolic blood pressure (BP) and heart rate in the supine and standing positions, and at the end of isometric work, during placebo run-in and urapidil and clonidine treatment periods

	Placebo period			Urapidil period		Clonidine period	
	Start	Week 3	Week 6	Week 3	Week 6	Week 3	Week 6
Systolic BP [mmHg]							
Supine	172±18	172±21	175±24	165±18	169±23	154±21*	158±19*
Standing	171±18	168±18	168±23	158±21	160±23	148±15*	151±20*
Isometric	–	192±20	194±20	178±19	186±26	173±19*	169±22**
Diastolic BP [mmHg]							
Supine	104± 7	106± 8	110± 8	104±10	105±11	98±11*	101± 9*
Standing	110± 6	113± 7	114± 6	106± 8**	108± 9*	101± 7***	104±10**
Isometric	–	126±11	128±10	122±14	125±16	114±13***	117±12***
Heart rate [beats/min]							
Supine	65± 7	67± 6	67± 7	71±11	70±11	66± 7	65± 6

$n = 11$, m±SD
*$= p < 0.05$, **$= p < 0.01$, ***$= p < 0.001$ } compared to the corresponding 6 week values in the run-in period

Table 2. Systolic and diastolic blood pressure (BP) and heart rate in the supine and standing positions, and at the end of isometric work, in the double-blind cross-over study

	Washout period	Treatment period			
		Urapidil		Clonidine	
		Week 3	Week 6	Week 3	Week 6
Systolic BP [mmHg]					
Supine	170±18	161±25	167±19	152±12**	155±19*
Standing	163±19	158±23	153±21	146±11*	149±19*
Isometric	188±20	178±21*	177±19*	170±16**	177±19*
Diastolic BP [mmHg]					
Supine	109± 9	104±10	106± 9	100± 7*	100± 9*
Standing	113± 9	107± 9*	106± 9*	103± 6**	102± 6**
Isometric	127±13	122±13	121±14	116± 7***	117±12***
Heart rate [beats/min]					
Supine	68± 7	71± 7	73±10*	66± 8	68± 7

$n = 11$, m±SD
*$= p < 0.05$, **$= p < 0.01$, ***$= p < 0.001$ } compared to the corresponding six week values in the run-in period

sphygmomanometer. The time of the visits was between 5 and 6 p.m. Blood pressure in the left arm was measured in the supine and standing positions. The supine blood pressure was measured after 10 min rest in recumbency and the standing blood pressure 2 min after assumption of the erect position. Three readings were made 1 min apart in the supine position and the average was used for calculation of the results. The first and fifth phases of the Korotkoff sounds were used as the criteria for the systolic and diastolic pressures, respectively. The pulse rate was recorded after taking the blood pressure measurement in the supine position, by palpation of the wrist for 60 s.

The patients performed the isometric sustained handgrip exercise after measurements of the supine and standing blood pressures. Blood pressure was measured 3.5–4 min after the start of 30% of the maximal capacity of handgrip work, carefully avoiding the Valsalva effect. The patient was prone during the test.

At each visit during the study, any side-effects due to the treatment were evaluated by use of a doctor-completed questionnaire relevant to the side-effects of urapidil and clonidine. Patient compliance was indicated by deviation of the result by no more than 5% from the expected result in all 11 patients.

Table 3. Side-effects of the treatment during the different periods of the study

Side-effect	Placebo	Dose titration		Treatment periods		Wash-out	
		Urapidil	Clonidine	Urapidil	Clonidine	Urapidil	Clonidine
Drowsiness			2		1		
Dry mouth			3		1		
Dizziness	1			1			2
Nasal congestion			1		1		
Cold extremities					1		
Headache	1		1				1

$n = 11$

Statistical Analysis

The paired t-test was used for comparison of the mean values of blood pressure and heart rate.

Results

Blood Pressure and Heart Rate

Eleven patients completed the study. The changes in pooled mean supine, standing and isometric blood pressures and heart rate during different phases of the study are shown in Fig. 3 and Tables 1 and 2. During the dose-titration period urapidil only lowered standing diastolic blood pressure ($p <$ 0.05–0.01), whereas clonidine reduced both supine and standing pressures as well as the pressure during isometric work (Table 1). During the urapidil treatment period, there was again a statistically significant reduction in the standing diastolic pressure ($p < 0.05$), and in systolic blood pressure at the end of isometric work ($p < 0.05$), when the values were compared with those measured at the end of placebo treatment. During the clonidine treatment period, decreases both in supine and standing as well as isometric blood pressures were evident compared to the values at the end of placebo treatment (Table 2).

Urapidil increased heart rate by 5 beats/min ($p < 0.05$) after 6 weeks of treatment.

During urapidil treatment, one patient out of the total of 11 (9%) became normotensive, defined as a supine diastolic pressure below 95 mmHg. The corresponding figure during clonidine treatment was 3 patients (27%).

Side-Effects

The side-effects of the treatments are listed in Table 3. Urapidil generally, caused fewer side-effects than clonidine. No drop-outs due to side-effects occurred. Routine laboratory tests during Weeks 0, 6, 10, 16, 23 and 29 revealed a slight elevation of serum alanine aminotransferase at each visit in 1 patient. No clinical signs of hepatic disease were observed in him. All other laboratory tests were normal.

No significant change in heart volume in chest X-rays could be seen during the study.

Discussion

The antihypertensive effect of urapidil is believed to be the result of decreased peripheral vascular resistance, mainly due to its inhibitory effect on postsynaptic alpha$_1$-adrenoceptors [4]. In addition, animal experiments have shown that urapidil, like clonidine, lowers sympathetic tone by stimulation of central alpha$_2$-adrenoceptors [4].

The relative importance of the two mechanisms is unclear, although recent evidence suggests that urapidil, in contrast to clonidine, may exert its hypotensive effect mainly via a peripheral mechanism [5].

Controlled clinical studies of the efficacy of urapidil in the treatment of hypertension are few [6–8]. There have been reports of 2 double-blind comparisons of the antihypertensive effects of clonidine and urapidil [6, 8]. After a one-week run-in period, treatment either with urapidil 60–90 mg daily or clonidine 0.5 mg daily for 4 weeks resulted in a substantial and similar reduction in blood pressure in both treatment groups. Our trial design employed was a comparison of the effects of two levels of fixed doses. The doses were chosen on the basis of earlier clinical studies [6–8, 9]. Keeping this in mind the very modest antihypertensive effect of urapidil in the present study was suprising. Use of a different trial design may be one explanation. The present study included a six-week placebo period and a double-blind cross-over comparison of the effects of the two drugs. By contrast, the studies mentioned above were based on groups treated in parallel [6, 8]. An alternative explanation may be use of too low a dose of

urapidil in the present study, since daily doses of up to 300 mg urapidil have been reported (Stumpe K. O., personal communication). On the other hand, the average daily dose of 48 mg urapidil proved to be sufficient in one multicentre study [9].

The modest antihypertensive effect of urapidil in the present study requires confirmation in further controlled clinical trials. The present results do, however, fit well with our preliminary findings on the combined effects of prazosin and clonidine in hypertensive out-patients at rest, and during isometric or dynamic exercise. In those circumstances that drug combination was ineffective and had a weaker antihypertensive effect than, for example, the combination of prazosin and atenolol. It is noteworthy that urapidil has been postulated to act on the one hand like clonidine and on the other hand like prazosin [4].

In short, in the doses employed, urapidil had a weaker antihypertensive effect and fewer side-effects than did clonidine.

Acknowledgements. The study was supported by Star Ltd., Tampere, Finland and Byk-Gulden Ltd., Konstanz, Federal Republic of Germany.

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Received: July 18, 1984
accepted in revised form: October 11, 1984

Eero Kanniainen, M.D.
Department of Medicine
Kemi Central Hospital
Kauppakatu 25
SF-94100 Kemi 10, Finland