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Pharmacodynamics and Pharmacokinetics of Urapidil in Hypertensive Patients: A Crossover Study Comparing Infusion with an Infusion-Capsule Combination

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Summary. The pharmacokinetics and haemodynamic effects of infused urapidil and an infusion-capsule combination were followed to study the correlation between the serum urapidil level and the blood pressure. Prior to urapidil administration, basal blood pressure and heart rate were measured for 16 h in 12 male hypertensive patients. Six patients received infusions lasting for 4 h of urapidil 10, 2.5 and 5 mg/h. Six patients were infused with urapidil 10 mg/h for 4 h and 2 h after the end of the infusion each took a 60-mg capsule. After a 5 day washout period the procedures were crossed over. A maximum serum urapidil level of 625 ± 232 ng/ml was achieved at the end of the 10 mg/h infusion, when the fall in blood pressure was 37/21 mmHg. During the 2.5 and 5 mg/h infusions the serum urapidil level was 330 and 420 ng/ml, respectively, and the corresponding decreases in blood pressure were 28/16 mmHg and 31/8 mmHg. Although the urapidil concentration 1 hour after beginning the infusion was only 184 ± 89 ng/ml a near maximal blood pressure decrease had already occurred 33 ± 9/20 ± 8 mmHg, whereas, 1 h after the end of the infusion the reduction in blood pressure was only 10 ± 12/3 ± 8 mm, with a urapidil concentration of 358 ± 120 ng/ml. During the plateau phases of both the infusion and infusion-capsule treatments the falls in blood pressure followed the serum urapidil levels. Only in the initial rising and final falling phases of the treatments were the pharmacodynamics and pharmacokinetics of urapidil not correlated.

Key words: urapidil, hypertension; alpha-adrenoceptor blocker, antihypertensive agent, pharmacodynamics, pharmacokinetics, adverse effects

Urapidil is a new antihypertensive drug belonging to the phenyl-piperazines [9]. Drugs of this class not only act as antihypertensive agents but they also show centrally inhibitory effects as well [2, 15, 17, 18]. Urapidil combines largely selective blockade of the post-synaptic alpha$_1$-receptor, resulting in a decrease in peripheral resistance, with an effect on sympathetic cardiovascular regulation. Although the actions of urapidil on the central nervous system are not completely understood, a sympathetic mechanism appears to be an important component of its activity. Urapidil reduces the hypertensive response to occlusion of the carotid arteries in concentrations which are not themselves antihypertensive, and, compared to phentolamine, it has a stronger antihypertensive effect and causes less pronounced peripheral alpha$_1$-blockade [15].

Studies of the correlation between the dose of urapidil and its serum concentration have shown that an increase in serum concentration is roughly correlated with a fall in blood pressure [4, 7, 8, 10]. A dose dependent increase in the pharmacodynamic effect after a 14-h infusion of 32.5, 65 and 130 mg urapidil in a cross-over design has been reported [8]. However, after discontinuation of the urapidil infusion, an immediate increase in blood pressure occurred, despite a persisting therapeutic serum level of urapidil.

The present investigation was designed to examine the discrepancy between the pharmacodynamic action and the serum urapidil level in the initial rising and final falling sections of the serum urapidil concentration curve.

Patients and Methods

Patients, Design and Protocol

The basal blood pressure and heart rate in 12 male hypertensive patients (170 ± 7/105 ± 3 mmHg), aged 53 ± 7 years and weighing 73 ± 10 kg, were measured hourly for 16 h on the day before treatment. Two dos-

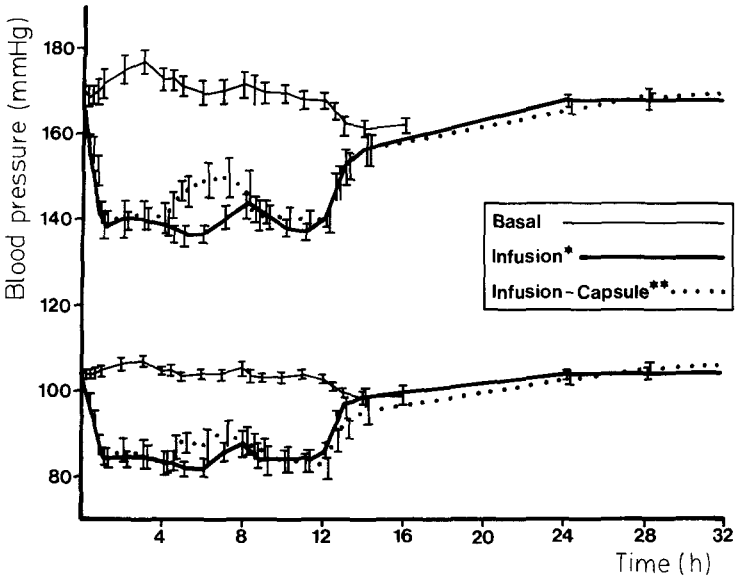

Fig. 1. Systolic and diastolic blood pressure before and after urapidil infusion and infusion-capsule administration. * Urapidil infusion: 0–4 h = 10 mg/h, 4–8 h = 2.5 mg/h, 8–12 h = 5 mg/h; ** Urapidil infusion-capsule: 0–4 h = 10 mg/h; 6 h = 60 mg capsule; $n = 10$; mean ± SEM

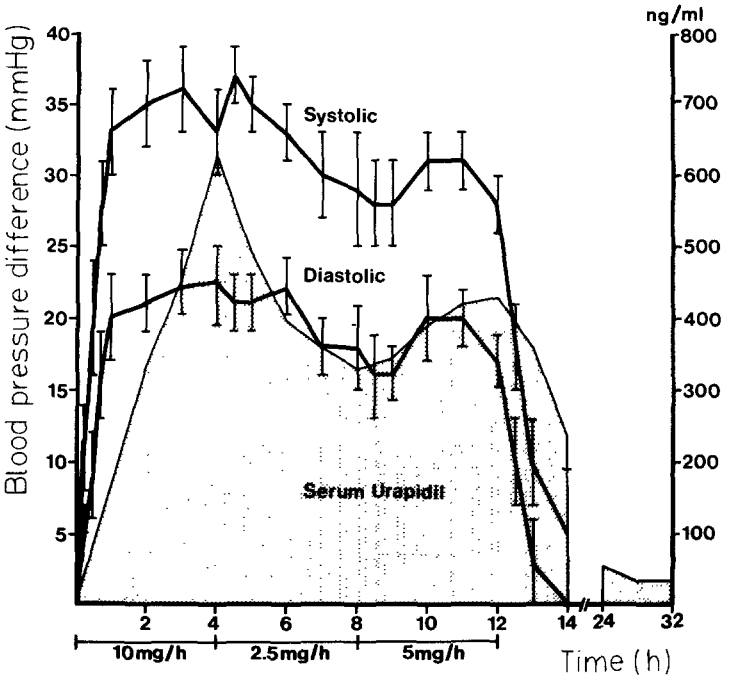

Fig. 2. Decreases in systolic and diastolic blood pressure (difference from basal values) during and after urapidil infusion. *Upper curve* = systolic BP, *lower curve* = diastolic BP, *shadowed area* = serum urapidil concentration; $n = 10$; mean ± SEM

ing procedures were carried out according to an open, randomised, cross-over design. On the first day of urapidil administration, procedure 1 was initiated in 6 patients, who received infusions of urapidil 10, 2.5 and 5 mg/h for 4 h. The second group of 6 patients underwent procedure 2, consisting of infusion of urapidil 10 mg/h for 4 h, and 2 h after ending the infusion administration of a 60 mg capsule. The infusion rates were chosen to produce similar serum urapidil concentrations in both procedures. After a washout period of 5 days the procedures were crossed over. Blood 3 ml was collected every hour during the first 14 h of the study, and at 24, 28 and 32 h, for the HPLC determination of plasma urapidil and its main metabolite, parahydroxy-urapidil. Blood pressure and heart rate were measured as blood was sampled and in addition every 15 min during the first hour of the 10 mg infusion and 30 min, after each change in the infusion.

Analytical Methods

Urapidil and its main metabolite, parahydroxy-urapidil, were measured by HPLC [14]. Blood samples

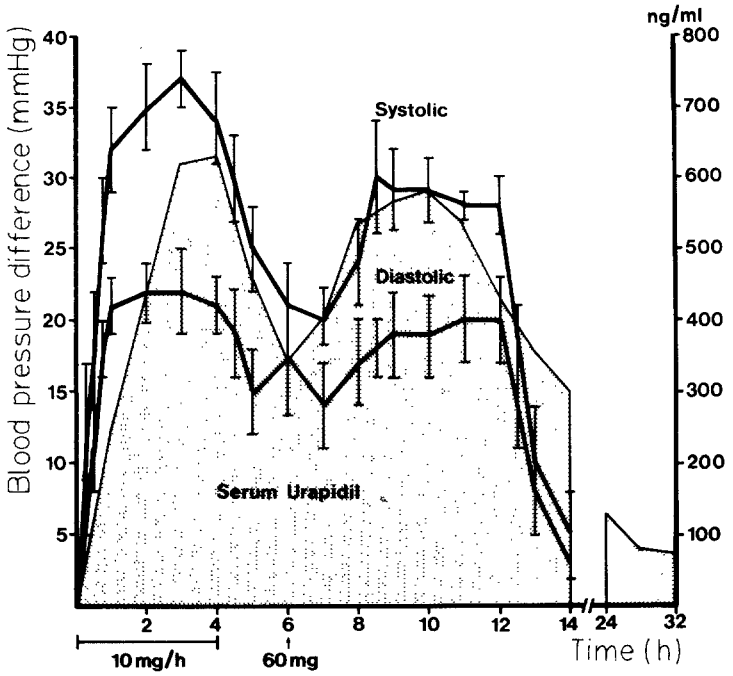

Fig. 3. Decreases in systolic and diastolic blood pressure (difference from basal values) during and after urapidil infusion-capsule administration. *Upper curve* = systolic BP, *lower curve* = diastolic BP, *shadowed area* = serum urapidil concentration; $n = 10$; mean ± SEM

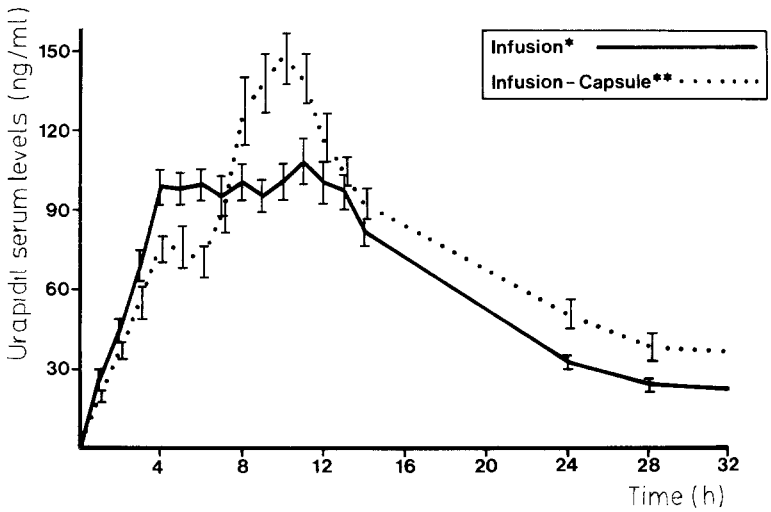

Fig. 4. Parahydroxy-urapidil level in serum (metabolite M_1) during infusion and infusion-capsule procedures. * Urapidil infusion: 0-4 h = 10 mg/h, 4-8 h = 2.5 mg/h, 8-12 h = 5 mg/h; ** Urapidil infusion-capsule: 0-4 h = 10 mg/h; 6 h = 60 mg capsule. $n = 10$; mean ± SEM

were centrifuged within 30 min of withdrawal and the serum frozen at −18 °C until analysed.

Values in the text are given as mean ± SD.

Results

The systolic and diastolic blood pressures before and after the urapidil infusion and the combined infusion-capsule application are shown in Fig. 1. The 10 mg/h infusion during the first 4 h caused an almost maximal fall in systolic and diastolic blood pressure (BP) after the initial hour of infusion. The blood pressure remained at that level despite changing the infusion rate to 2.5 and 5 mg/h. After cessation of the 10 mg/h infusion (before giving the capsule), both the systolic and diastolic blood pressures increased, but they again fell to the infusion level 2 h after capsule administration. Immediately after the end of the infusion and 6 h after the capsule the blood pressure began to fall and it had returned to its pretreatment level within 2 h.

To compare the pharmacokinetics with the pharmacodynamics during the infusion of urapidil the serum urapidil concentration (shadowed area) was superimposed on the decreases in the systolic and diastolic pressures (difference from basal values; Fig. 2.). In general, there was a close correlation between the blood pressure decrease and the serum urapidil level. The maximum serum urapidil level of

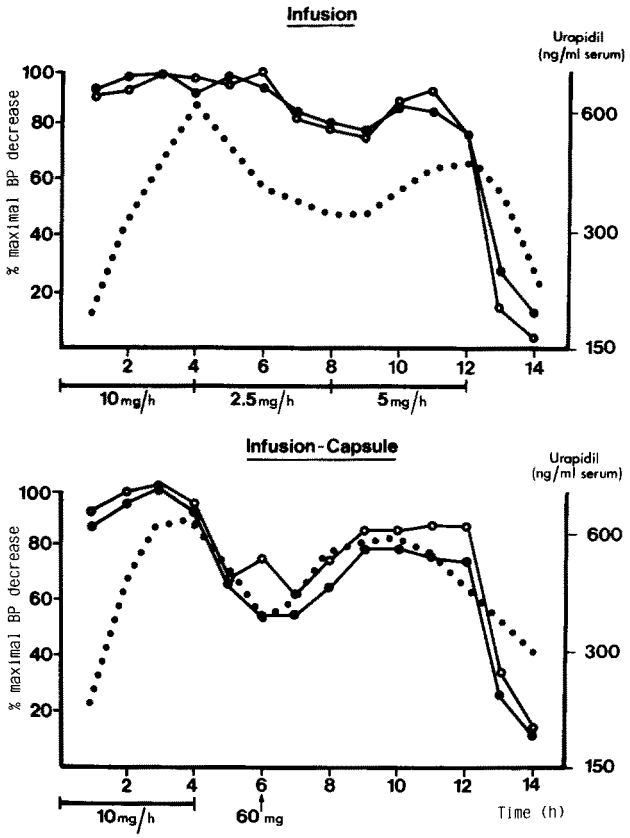

Fig. 5. Comparison between serum urapidil concentration and decreases in systolic and diastolic blood pressures (BP). The latter are expressed as % differences from the mean maximal falls in systolic (●—●) and diastolic (○—○) blood pressure during the two different treatments. Mean serum urapidil (· · · · ·) concentration. $n = 10$

625 ± 232 ng/ml at the end of the 10 mg/h infusion corresponded to the maximal decrease in blood pressure of $37 \pm 5/21 \pm 7$ mmHg 4.5 h after beginning the 10 mg/h infusion. The blood pressure decreases ranged from 28–37/16–22 mmHg during the three infusion periods. Divergence from the correlation between the serum urapidil level and the pharmacodynamic effect occurred in the initial inclining and final declining sections of the serum urapidil-time curve. Although the serum concentration 1 h after the infusion was begun was only 184 ± 89 ng/ml, there was a near maximal decrease in blood pressure of $33 \pm 9/20 \pm 8$ mmHg. The opposite effect was apparent in the final declining part of the serum urapidil curve, where 1 h after the end of the infusion the serum urapidil was 358 ± 120 ng/ml and the decrease in blood pressure was only $10 \pm 12/3 \pm 8$ mmHg.

Comparison of pharmacokinetics with pharmacodynamics during the infusion - capsule sequence again showed a close correlation between the falls in systolic and diastolic blood pressure (differences from basal values) and the serum urapidil concentration (shadowed area, Fig. 3). Administration of the capsule resulted in a second urapidil peak 10 h after beginning the test (maximum 578 ± 139 ng/ml); the maximum fall in blood pressure during procedure 2 was $34 \pm 8/20 \pm 10$ mmHg. Similar disparities in the correlation between serum urapidil and blood pressure in the initial inclining and final declining sections of the serum urapidil-time curve occurred during the combined infusion-capsule treatment, as were observed after the infusion alone.

The serum concentration of the main metabolite, parahydroxy-urapidil, during the infusion and infusion-capsule treatments is compared in Fig. 4. A steady-state of approximately 100 ng/ml was achieved with the infusion procedure. During the combined infusion-capsule sequence the metabolite rose to a maximum of 148 ± 31 ng/ml by 4 h after the capsule application.

There was no difference in the heart rate during either the infusion or the capsule-infusion procedures as compared to the basal measurements. Due to pronounced orthostatic dysregulation 2 of the 12 patients originally included did not complete the study. During the infusion procedure 3 of the remaining patients complained of side-effects; 1 patient experienced headache and dry mouth, 1 had headache and nausea, and a third suffered headache, fatigue and dry mouth. During the infusion-capsule procedure one patient complained of headache and dry mouth and another of fatigue and nausea. A causal relationship between these side-effects and the relatively high dose may be assumed.

Discussion

The pharmacokinetics of urapidil have been examined in a series of studies involving both intravenous and oral administration to normotensive volunteers, hypertensive patients [4, 8, 10, 13, 20], older patients [12] and patients with impaired kidney and liver function [1, 6]. The AUC has been found to be proportional to the applied dose [20]. No changes due to impaired kidney and liver function were found [1, 6], although a reduction in clearance in elderly patients has been observed [12]. Some authors have reported a correlation between side effects and the dose of urapidil [11].

The serum urapidil concentration and the decreases in systolic and diastolic blood pressure are visually compared in Fig. 5. Although the limited number of values in the rising and falling parts of the haemodynamic effects and concentration curves prohibits numerical analysis, there is a definite dis-

parity between the haemodynamic effects and the serum urapidil concentration. It is unlikely that the time course of the main metabolite, parahydroxy-urapidil, can account for the disparity, since experiments on the isolated vas deferens of the rat have shown that the metabolite is 100 times less vasoactive than urapidil [19]. A discrepancy in the free and total serum urapidil concentration is a more likely explanation for the lack of correlation [8].

The measurement of many drugs in blood does not allow accurate assessment of their effectiveness. This phenomenon occurs with MAO inhibitors, reserpine, anticholinesterases and anticancer drugs, which act irreversibly with effects persisting long after the drug has left the tissues. Other drugs are bound to specific tissues. Propranolol, for instance, is bound up to 15-fold in brain and other tissues [5]. It is also stored presynaptically and is released during nerve stimulation [3]. Wellstein et al. have concluded that, in the case of propranolol, the discrepancy between the concentration kinetics and effect kinetics could be explained by the receptor interaction of propranolol [16]. This may be the case with urapidil as well, and further studies directed at the target site might clarify the disparity between the haemodynamic effect and the serum urapidil level in the rising and falling parts of the serum urapidil-time curve.

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