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Pharmacodynamics and Pharmacokinetics of Three Different Doses of Urapidil Infused in Hypertensive Patients

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Summary. The study was designed to follow the haemodynamic effects and pharmacokinetics under steady-state conditions of three different doses of urapidil infused continuously. Nine male hypertensive patients received three randomly assigned intravenous infusions of 32.5, 65 and 130 mg urapidil, over 14 h during 6 consecutive days, in a change-over fashion. Blood pressure and heart rate were measured over a period of 28 h after the infusion began and were compared with a reference profile obtained prior to the treatment periods. Urapidil and its main metabolite, parahydroxylated urapidil, were also determined for 28 h after the infusion began using HPLC. The 32.5 mg dose of urapidil caused a maximum decrease in systolic blood pressure of 33 ± 8 mmHg, the 65 mg dose a maximum decrease of 39 ± 12 mmHg and the 130 mg dose a maximum decrease of 50 ± 12 mmHg. The 32.5 and 65 mg doses resulted in similar serum urapidil concentrations, with maximum levels in the 100 to 200 ng/ml range, and the 130 mg dose caused a maximum level approximately four times that achieved with the 32.5 mg dose. The serum concentration of parahydroxy urapidil was proportional to the corresponding dose of urapidil. Four patients reported mild headache, fatigue, weakness, pressure in the head, perspiration and orthostatic dysregulation. The side-effects were probably drug related but required no specific therapy. In summary, the 32.5 mg dose of urapidil resulted in a pronounced decrease in blood pressure. The average pressure reduction over the 14-h infusion period showed further dose-dependent increases after the 65 and 130 mg doses. In severe hypertension, the 130 mg dose can be employed, since it does result in a further, significantly larger decrease in blood pressure.

Key words: urapidil; pharmacodynamics, pharmacokinetics, hypertension

Urapidil is a new antihypertensive drug with α_1-adrenoceptor blocking activity [6], which reduces blood pressure by decreasing the peripheral vascular resistance [1, 3, 10]. The drug has proved to be effective both in long-term treatment with capsules [4] and during hypertensive crises when it has been administered as a bolus injection and as an infusion. Schuster [12] showed a reduction in blood pressure of 48 ± 34/34 ± 18 mmHg after bolus injection of 5-40 mg urapidil and of 64 ± 23/38 ± 8 mmHg after infusion of total doses of urapidil ranging from 5.8-63.6 mg. The present study was designed to follow the haemodynamic effects and pharmacokinetics of urapidil 32.5, 65 and 130 mg infused over 14 h in the same patients according to a three period change-over design.

Patients and Methods

Patients, Design and Protocol

Nine male hypertensive patients (178 ± 11/110 ± 5 mmHg) aged 54 years (range, year 47-68), weighing 88 kg (range 83-90 kg) received three randomly assigned intravenous infusions of 32.5, 65 and 130 mg urapidil over 14 h, on six consecutive days, in a change-over fashion. On the day preceding each urapidil infusion, blood pressure and heart rate were measured over 14 h as reference values. Shortly before 6 a.m. an indwelling cannula was inserted into an antecubital vein in each arm. At 6 a.m. 7 ml blood was collected and the infusion was commenced at 10 ml/h. The dose was dissolved in 140 ml isotonic glucose. Blood samples were taken from the contralateral arm at 8, 10 and 12 a.m., 6, 8 and 10 p.m., and at 6, 8 and 10 a.m. on the following morning. Blood pressure and heart rate were measured hourly from 6 a.m. until 10 p.m., and at 6, 7, 8, 9 and 10 a.m. on the

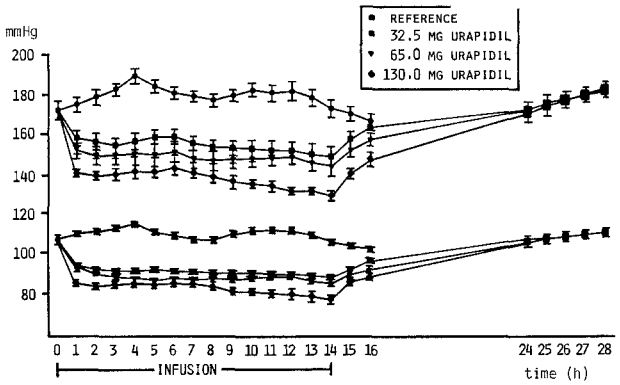

Fig. 1. Systolic and diastolic blood pressure before and after i.v. infusion of urapidil. Means ± SEM, $n = 9$. Urapidil 32.5 mg ■—■ 65.0 mg ▲—▲, 130 mg ◆—◆

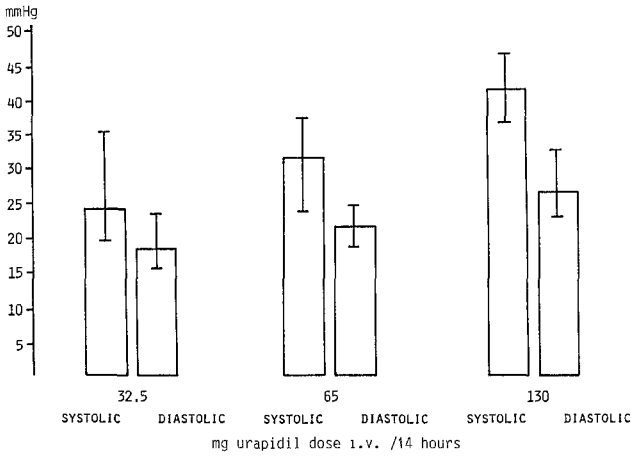

Fig. 2. Average hourly decrease in blood pressure during 14-h urapidil infusion compared to reference profile median and nonparametric 95% confidence limits, $n = 9$

following morning. The use of other vasoactive drugs was not permitted during the infusion and monitoring periods. All side-effects were documented, recording the time of occurence and possible relationship to treatment. The patients were informed of the nature of the investigation and gave their written consent to participation in the study.

Analytical Methods

Urapidil and metabolite determination. Blood samples were centrifuged within ½ h of collection and the serum was frozen at −18 °C until assayed. All reagents were of analytical grade. Urapidil and its main metabolite, parahydroxy-urapidil, were determined by HPLC [9].

Biostatistical Methods

The time profiles of pharmacokinetics and pharmacodynamics have been expressed as the mean ± SEM; changes in blood pressure and heart rate as the mean ± SD. To characterize the hypotensive effect of urapidil, the area between the reference profile and the treatment profile of the 14-h infusion period (AUC) was employed. Median and nonparametric 95% confidence limits [5] are given for AUC/14, which represents the time-averaged blood pressure decrease during the infusion. The Wilcoxon-Pratt test was used to detect significant differences in blood pressure and heart rate between the various doses of urapidil.

Results

The systolic and diastolic blood pressures during the infusion of 32.5, 65 and 130 mg urapidil are com-

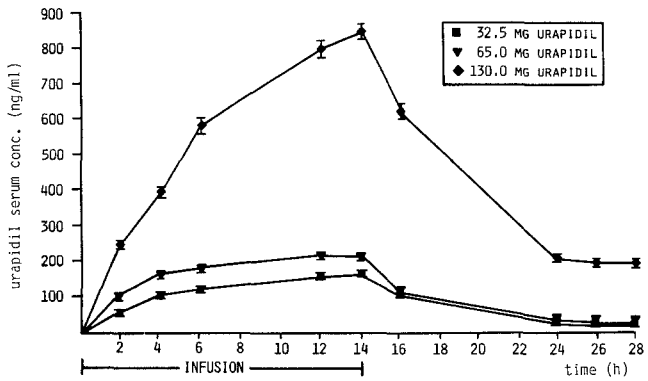

Fig. 3. Serum urapidil concentration after intravenous infusion of urapidil. Means ± SEM, $n = 9$. Symbols see Fig. 1

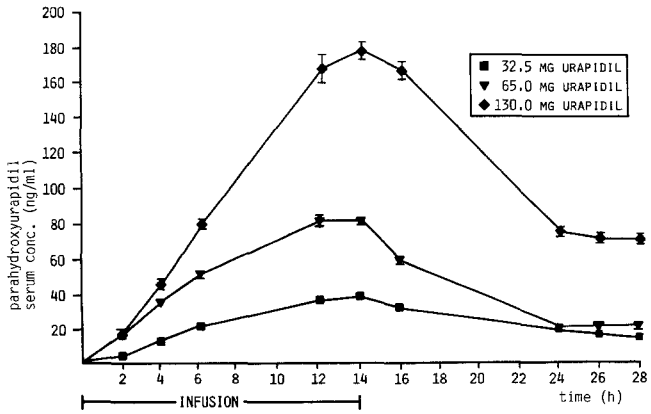

Fig. 4. Parahydroxy-urapidil in serum after intravenous infusion of urapidil. Means ± SEM, $n = 9$. Symbols see Fig. 1

pared to the reference profile in Fig. 1. After 1 h of infusion approximately two-thirds of the maximal reduction in blood pressure was achieved. The maximum blood pressure reduction occurred 4 h after starting the infusion of 32.5 and 65 mg urapidil. With the 130 mg dose two peak falls in blood pressure occurred 4 and 12 h after beginning the infusion. The 32.5 mg dose caused a maximum decrease of 33 ± 8/23 ± 6 mmHg (mean ± SD), the 65 mg dose a maximum decrease of 39 ± 12/27 ± 6 mmHg, and the 130 mg dose a maximum decrease of 48 ± 5/29 ± 6 mmHg after 4 h and 50 ± 12/31 ± 8 mmHg after 12 h.

The average fall in blood pressure during the 14-h infusion period is shown in Fig. 2. Values were obtained by calculating the differences between the areas under the treatment curves and the reference profile and dividing by 14. Individual falls in blood pressure are summarized by median and nonparametric 95%-confidence limits [5]. For the 32.5, 65 and 130 mg doses of urapidil, the following results were obtained: 24 (19,35)/18 (15,23) mmHg, 31 (23,37)/21 (18,24) mmHg and 41 (36,46)/26 (22,32) mmHg, respectively. The data show that the higher doses of 65 and 130 mg result in further decreases in blood pressure compared to the 32.5 mg dose. The additional reduction in systolic blood pressure was more pronounced than that in diastolic blood pressure. The effects of the highest dose on systolic and diastolic blood pressures were significantly ($p < 0.01$) greater than those of the two lower doses.

The serum urapidil concentrations following the intravenous infusions are shown in Fig. 3. Both the 32.5 and 65 mg doses resulted in similar serum concentrations with maximum levels in the 100 to 200 ng/ml range. The 130 mg dose produced a level approximately four times that achieved with the 32.5 mg dose; the maximum was approximately 800 ng/ml.

The serum concentration of the metabolite parahydroxy-urapidil during the infusion of each of the three doses is illustrated in Fig. 4. The serum concentrations were approximately proportional to the dose. The maximum concentrations were 30, 70 and 170 ng/ml after 32.5, 65 and 130 mg urapidil, respectively. Heart rate was significantly ($p < 0.05$) decreased by approximately 5 ± 5 beats/min in the 8th to 12th hours after the infusion began. The decrease was not dose dependent.

Four patients reported mild headache, fatigue, weakness, pressure in the head, perspiration and orthostatic dysregulation, which were probably drug related but required no specific therapy.

Discussion

The study was designed to investigate the pharmacodynamic responses to increasing intravenous doses of urapidil. Based on a serum urapidil half-life of about 2.5 h [14], a steady-state serum concentration was anticipated 12–14 h after starting the infusion, a 14-h infusion period was chosen. The doses of 32.5, 65 and 130 mg urapidil were selected to achieve steady-state concentrations in healthy volunteers of approximately 200, 400 and 800 ng/ml, respectively. In addition to previous clinical studies, the main serum metabolite, parahydroxy urapidil, was also determined.

The results show that the blood pressure reduction reached a maximum long before the steady-state serum urapidil was achieved. Although the blood pressure lowering effect was already pronounced after the lowest dose of urapidil of 32.5 mg, the average blood pressure over the 14-h period showed that further dose-dependent falls were induced by the 65 and 130 mg doses.

The reductions both in systolic and diastolic blood pressure were comparable to the values of 48 ± 38/34 ± 18 mmHg reported by Schuster and Trieb after an i.v. bolus of 20–40 mg urapidil [12]. The maximum falls in blood pressure produced here by the infusions of 32.5 and 65 mg urapidil were 33 ± 8/23 ± 6 mmHg and 39 ± 12/27 ± 6 mmHg, respectively. The difference in blood pressure reduction between the two doses was minimal, as was the difference in serum urapidil after these two doses. The 130 mg dose caused a substantially larger maximum decrease in blood pressure of 50 ± 12/31 ± 8 mmHg. The serum urapidil after the 130 mg dose was approximately four times higher than after the 32.5 mg dose. The same ratio applied to the main metabolite, parahydroxy-urapidil. Previous experiments on the isolated vas deferens of the rat have shown that parahydroxy-urapidil is 100-times less vasoactive than urapidil [13].

The maximum fall in blood pressure 4 h after the infusion began may be attributed to reversal of the normal peak circadian blood pressure at 10 a.m. by the treatment with urapidil. A second maximum decrease 12 h after starting the infusion was seen following the 130 mg dose, and it may be attributed the normal slight circadian increase which occurs at that time. Minimal side effects occurred, which were not dose related. Slight but significant decreases in heart rate occurred at 10 a.m. and in the late afternoon. Similar neglibible decreases in heart rate have been reported by Bigge and Leibetseder [2, 7].

The serum metabolite levels over 28 h showed good dose proportionality, but this applied to urapi-

dil only during the first 2 h of the infusion. For unknown reasons the 62.5 mg dose produced only 65(62-69)% of the expected AUC, whereas the 130 mg dose resulted in 131(120-140)% of the AUC anticipated on the basis of the 32.5 mg dose. The peak concentration of about 800 ng/ml following the 130 mg dose was in accordance with the serum urapidil level expected in healthy volunteers. It appears that the serum urapidil levels following the highest dose had not reached a plateau after 14 h.

It is interesting that the overnight decrease in the serum urapidil had a half-life of 4.8 h following the lowest and the highest doses and 3.2 h following the mid-dose. During the second day of each treatment period, the serum urapidil concentrations declined only marginally. This has not been observed in previous pharmacokinetic studies in which lower doses of urapidil were given as intravenous bolus injections. It would be of interest to explain the immediate increase in blood pressure despite persisting therapeutic serum levels of urapidil after discontinuation of the urapidil infusion. Perhaps work directed at the urapidil receptor may clarify this point.

In summary, 32.5 mg urapidil infused over a period of 14 h was an effective dose, reducing blood pressure by an average of 24/18 mmHg during the infusion. This effect was dose-dependently increased to 31/21 and 41/26 mmHg after 65 and 130 mg urapidil, respectively. The 130 mg dose may be employed in severe hypertension, since the blood pressure lowering effect of this dose significantly ($p < 0.01$) exceeded that of the lower dose.

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