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Originals

The effect of Urapidil on responses to phenylephrine, angiotensin and isoprenaline in man

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Summary. Intravenous urapidil, 40 mg bolus followed by an infusion of 18 mg · h^{-1} for 2 h was administered to 6 female non-patient volunteers. Randomised cumulative dose response curves to angiotensin, phenylephrine and isoprenaline were performed before and commencing 30 min after the start of the infusion of urapidil. Urapidil significantly reduced supine systolic blood pressure, 118.5 mm Hg to 105.3. The diastolic blood pressure was not significantly reduced, heart rate was not affected. Urapidil did not affect the responses to angiotensin or isoprenaline. Urapidil inhibited the pressor response to phenylephrine. The dose required to increase systolic blood pressure by 20 mm Hg increased from 156.9 μg · min^{-1} before to 685 μg · min^{-1} during urapidil; Dose ratio from individual values of 4.58. Urapidil concentrations were not significantly different before and after each agonist infusion. It is concluded that urapidil has α_1-adrenoceptor blocking activity in man without any non specific vasodilator action and that it is devoid of beta adrenoceptor blocking action.

Key words: Urapidil; phenylephrine, angiotensin, isoprenaline, dose-response, pharmacodynamics

Urapidil is an antihypertensive drug which is derived from arylpiperazine. Animal investigations suggest a complex mechanism of the antihypertensive effect. Suggestions have included α_1-adrenoceptor blocking activity demonstrated in animal studies [Sanders et al. 1985; Van Zwieten et al. 1984], a weak β_1 adrenoceptor blocking activity found in animal models by several authors [Freissmuth et al. 1984; Rassier et al. 1986; Verbene and Rand, 1985] and a central depression of the sympathetic 'tone', which, unlike clonidine does not depend on the excitation of the alpha$_2$ receptor [Van Zwieten et al. 1984; Van Zwieten et al. 1985a, 1985b]. There is evidence that urapidil has a central action that is mediated by stimulation of serotonin 1A receptors [Gillis et al. 1988; Kolassa et al. 1989]. Peripheral α_1-blocking activity has been demonstrated in man [Gerber et al. 1985; Leonetti et al. 1986], whereas the evidence for β-adrenoceptor blocking activity is marginal in man [Jamieson et al. 1986]. The pharmacological action of urapidil is not yet fully assessed in man, particularly any part played by a beta blocking activity and its central action.

The objective of the study was to define at therapeutic urapidil serum concentration the extent of and the ratio between alpha and beta blocking activities of urapidil. Some of these studies have previously been briefly reported [Renondin et al. 1988].

Methods

The study included 6 healthy female volunteers (mean age 20.5 (1.1) y; mean weight 67.1 (2.8) kg; mean height 173 (2.5) cm). Heart rate was recorded from a continuously running ECG, blood pressure by the London School of Hygiene sphygmomanometer calibrated to 111 mm Hg [Fitzgerald et al. 1982].

An intravenous cannula was inserted into a large vein in the left forearm. Subjects rested supine for 30 min and baseline heart rate (HR) and blood pressure (BP) were recorded. The three agonists (phenylephrine, angiotensin, and isoprenaline) were infused in random order with incremental doses.

The phenylephrine was commenced at 100 μg · min^{-1}, isoprenaline at 0.5 μg · min^{-1}, and angiotensin at 0.5 μg · min^{-1}. Each dose was infused for 4 min. The doses were increased on a logarithmic scale with increments of 2 or $\sqrt{2}$. The infusions of angiotensin and phenylephrine were stopped when the rise of the systolic blood pressure was more than 30 mm Hg or when the diastolic blood pressure (DBP) reached 110 mm Hg. The isoprenaline infusion was stopped when the heart rate increase exceeded 30 beats · min^{-1}. Between the infusions at least 15 min recovery was allowed before starting the next infusion in order to obtain a steady HR ± 6 beats · min^{-1}, DBP ± 6 mm Hg, compared to the baseline.

An intravenous bolus of urapidil 40 mg was administered over 5 min followed by an infusion of 18 mg · h^{-1} for 2 h, so that the predicted urapidil concentration would be about 1.0 μg · ml^{-1} representing the higher end of therapeutic range [Beltz et al. 1985]. After 30 min of urapidil infusion, the three incremental agonist infusions were repeated in the same sequence as that given prior to urapidil.

Heart rate and blood pressure were recorded each min throughout the infusions. Prior to each agonist infusion and at the

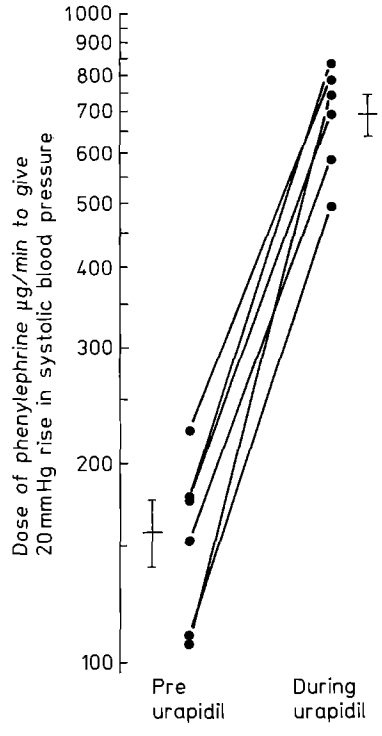

Fig. 1. The effect of urapidil on the pressor response to phenylephrine

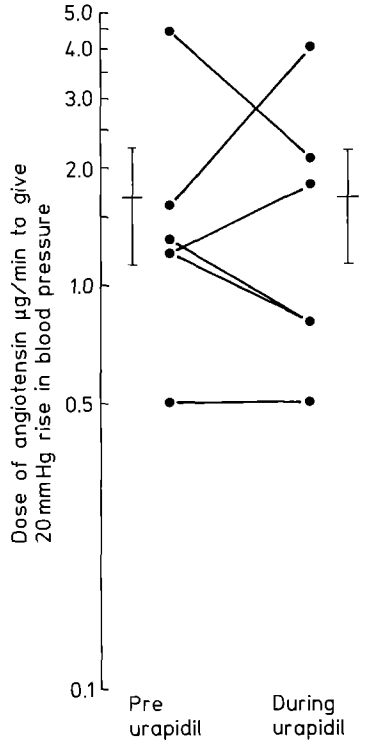

Fig. 2. The effect of urapidil on the pressor response to angiotensin

end of the maximum dose level, 5 ml of blood was withdrawn for urapidil level determination. Urapidil concentration was determined by HPLC at Byk Gulden [Kirsten et al. 1988].

The cumulative dose response curves for the 3 agonists were fitted according to quadratic functions. The dose response curves in the absence and the presence of urapidil were compared for any shift. Characteristic parameters were compared by 't test' and ANOVA, the level of alpha fixed at 5%.

The study was approved by University College and University College Hospital Ethics Committee and each subject underwent a thorough physical examination before entering into the study and gave their written consent.

Results

All six subjects completed the study. The individual laboratory values remained within the normal range. The effect of urapidil on blood pressure and heart rate after the 5 min bolus and 15 min of infusion showed a significant decrease in the systolic blood pressure (pre-urapidil 118.5 [3.6] mm Hg; during urapidil 105.3 [3.4] mm Hg; $P < 0.01$). Diastolic blood pressures, 62.3 (3.4) mm Hg and 57.5 (2.1) mm Hg respectively, were not significantly different, neither did the HR show any significant change (pre-urapidil 74.0 [2.6] beats $\cdot$ min^{-1}; during urapidil 76.8 [1.2] beats $\cdot$ min^{-1}).

Urapidil produced a highly significant shift in the dose response curve to phenylephrine. The dose of phenylephrine needed to produce a 20 mm Hg rise in systolic blood pressure prior to urapidil was 157 (18.2) µg $\cdot$ min^{-1}, and in the presence of urapidil 686 (52.1) µg/min, ($P < 0.001$), with a ratio calculated from individual values of the response to phenylephrine during and before urapidil of 4.58 (1.87) (Fig. 1).

There was no effect on the response to angiotensin by urapidil. A dose of 1.69 (0.56) µg $\cdot$ min^{-1} angiotensin was required to give a 20 mm Hg rise before urapidil and a dose of 1.66 (0.54) µg $\cdot$ min^{-1} (NS) in the presence of urapidil (Fig. 2).

Urapidil did not have any effect on the response of the HR to isoprenaline (Fig. 3). The dose of isoprenaline to give an increase in HR of 25 beats $\cdot$ min^{-1} prior to urapidil was 2.32 (0.42) vs 2.45 (0.54) µg $\cdot$ min^{-1} (NS) in the presence of urapidil.

The urapidil concentrations were not statistically different before and after each agonist infusion (Table 1).

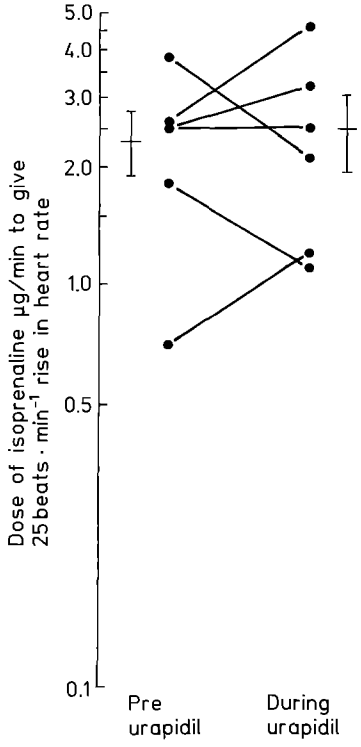

Fig. 3. The effect of urapidil on the heart rate response to isoprenaline

Table 1. Serum Urapidil Levels ($mg \cdot l^{-1}$) before and after agonist infusions ($n = 6$)

	Angiotensin		Phenylephrine		Isoprenaline	
	Pre	Post	Pre	Post	Pre	Post
Mean	1.224	1.190	1.224	1.562	1.337	1.578
(SEM)	(0.181)	(0.079)	(0.177)	(0.137)	(0.275)	(0.165)

Discussion

At doses giving serum concentrations corresponding to those achieved therapeutically, we have found evidence that intravenous urapidil specifically inhibits the response to exogenous α_1-adrenoceptor stimulation, since the dose-response curves with phenylephrine are shifted to the right whereas those with angiotensin are not affected, indicating the absence of any non specific vasodilator action. Other investigators have found evidence of alpha$_1$-blocking action. Leonetti et al. (1986) found α_1-adrenoceptor blocking activity acutely after 25 mg urapidil given intravenously, as did Gerber et al. (1985) after oral urapidil 30 mg b.i.d. for 4 weeks.

While earlier studies in animals demonstrated some β-blocking activity, we found no suggestion of a shift in the HR dose-response curves to isoprenaline, although we only utilised 6 subjects. This is, however, in accord with most other observations in human subjects as Belz et al. (1985) did not observe any effect on exercise induced HR increase after 75 mg intravenous urapidil, nor did Leonetti et al. (1986) after 4 weeks oral urapidil at 30 mg bd in hypertensive patients. Therefore it is improbable that β_1-adrenoceptor blocking activity contributes to the antihypertensive effect of urapidil. However, Jamieson et al. (1986) found that a 30 mg dose of urapidil intravenously in 10 normal volunteers produced an isoprenaline dose ratio of 1.77 which was suggested as almost significant ($P = 0.06$) but only a 1 tail 't' test was used.

The fall of the blood pressure from urapidil is mainly due to the decrease of the vascular resistance while, in contrast to vasodilators urapidil, does not affect HR [Prichard et al. 1989]. In the present study, there was no significant difference between HR before urapidil infusion and HR after 25 min urapidil infusion (74.0 [2.6] vs 76.8 [1.2] beats $\cdot$ min^{-1}). As there was no evidence of significant β-adrenoceptor blocking activity a central effect may explain this lack of reflex tachycardia [Prichard et al. 1989] and this is supported by the animal data [Kolassa et al. 1989].

Urapidil is a drug which has been shown in animals to have multiple actions that might account for its antihypertensive effect. In this study urapidil showed a specific alpha$_1$-blockade activity, which appears to be the main mechanism of the fall in blood pressure. However there was no change in heart rate, rather than an increase which might be expected with peripheral vasodilatation. This is compatible with a central component in the action of urapidil, as no peripheral beta-blocking activity was found. This is supported by investigations in animals which suggest a central effect of urapidil as discussed above.

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