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Short Communications

Acute Haemodynamic Effects of Urapidil in Patients with Chronic Left Ventricular Failure

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Summary. Urapidil, a new alpha$_1$-adrenoceptor blocking drug, has been shown to be effective in the treatment of hypertension. Ten normotensive patients with severe congestive heart failure were given Urapidil 25 mg i.v. twice in 15 min and the haemodynamic effects were measured.

There was a significant fall in systolic blood pressure (−16%), mean blood pressure (−13%), left ventricular end-diastolic pressure (−38%), mean pulmonary artery pressure (−31%) and wedge pressure (−40%). Total peripheral resistance fell by 25%, whereas pulmonary arteriolar resistance did not change significantly. Cardiac output increased by 22%.

The increase in cardiac output with decreasing peripheral resistance and LV pressures suggests that urapidil may be useful in the therapy of congestive heart failure.

Key words: urapidil; left ventricular failure, haemodynamic parameters

Urapidil, a new antihypertensive drug, lowers peripheral resistance by three main mechanisms: first, it is a postsynaptic α_1-antagonist; second, it reduces sympathetic tone by a non-clonidine-like central mechanism; and third, it exerts a direct central hypotensive action [1, 2]. A possible weak β_1-effect has also been suggested [3, 4]. Studies in animals and in humans have shown good efficacy and tolerability without any influence on biochemical variables [5, 6].

Because urapidil decreases peripheral resistance without increasing the heart rate and plasma renin activity it seems promising for the treatment of hypertension and of severe congestive heart failure. The present study was designed to investigate the acute haemodynamic effects of urapidil in patients with chronic left ventricular failure.

Patients and Methods

Ten male patients, aged 23 to 74 years (mean 53 years), with chronic left ventricular failure (NYHA Class III or IV) were studied during routine right and left heart catheterisation (Table 1).

Table 1. Clinical data

Patient	Age (years)	Sex	Diagnosis	Previous myocardial infarction	Ejection fraction (biplane angio)	Mitral insufficiency
1	62	Male	CAD[a], 1-Vessel disease	+	29%	+
2	47	Male	CAD, 3-Vessel disease	+	34%	−
3	56	Male	Dilated cardiomyopathy	−	30%	+
4	23	Male	Dilated cardiomyopathy	−	10%	−
5	61	Male	CAD, 3-Vessel disease	+	31%	+
6	44	Male	Dilated cardiomyopathy	−	36%	+
7	63	Male	CAD, 3-Vessel disease	+	32%	−
8	50	Male	CAD, 3-Vessel disease	+	24%	−
9	45	Male	CAD, 1-Vessel disease	+	23%	+
10	74	Male	CAD, 3-Vessel disease	+	34%	+

[a] coronary artery disease

Table 2. Effects of urapidil on haemodynamics in patients with chronic left heart failure

	Urapidil i.v. 25 mg		25 mg					
	Control		5 min		20 min		45 min	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Heart rate (beats·min^{-1})	81.3	15.5	82.9	15.0	80.1	16.3	78.4	17.8
Systolic blood pressure (mm Hg)	113.5	17.8	102.2	12.7**	97.0	13.6**	94.9	14.6**
Mean blood pressure (mm Hg)	89.3	10.7	81.0	6.9*	77.8	8.1**	77.3	11.4**
Mean right atrial pressure (mm Hg)	5.9	3.1	4.1	2.9*	4.3	2.3*	3.5	2.1*
Left ventricular enddiastolic pressure (mm Hg)	31.2	9.4	21.5	8.3**	20.3	8.7**	19.3	7.8**
Mean pulmonary artery pressure (mm Hg)	33.8	11.3	26.0	10.2**	23.5	9.7**	23.3	8.4**
Pulmonary capillary wedge pressure (mm Hg)	24.9	10.8	16.3	7.4**	14.0	7.2**	15.0	7.8**
Cardiac output (l·min^{-1})	4.59	0.67	5.27	1.05*	5.42	0.97*	5.58	1.11**
Pulmonary arteriolar resistance (dyn·s·cm^{-5})	157	100	136	105	132	66	116	57
Total peripheral resistance (dyn·s·cm^{-5})	1510	242	1255	302*	1161	277**	1126	301**
Plasma concentration urapidil (μg·ml^{-1})	-	-	0.647	0.371	1.135	0.648	0.766	0.332

* (**) = $p < 0.05$ (0.01)

The following criteria were used to select the patients: conventional therapy with digitalis and diuretics, but no treatment with other vasodilator agents; left ventricular ejection fraction <40%; and elevated LV enddiastolic pressure >20 mm Hg.

The aetiology of the congestive cardiac failure was ischaemic coronary artery disease (CAD) in 7 patients, based on a history of myocardial infarction and the demonstration of significant coronary artery lesions by coronary angiography (1- to 3-vessel disease). Three patients had dilated cardiomyopathy and normal coronary arteries. The resting ejection fraction (biplane ventriculography) ranged from 10-36% (mean 28±8%). In 5 patients relative mitral insufficiency was visible during biplane ventriculography. Left heart catheterisation was performed by the Sones or Judkins techniques, and right heart catheterisation was done with a 7 F, Swan-Ganz, flow directed thermodilution balloon catheter inserted via a brachial or femoral vein and positioned in the pulmonary artery.

Following angiography 15 to 30 min were allowed for the achievement of haemodynamic stability. Cardiac output (CO) was estimated in triplicate by the thermodilution technique. Direct measurements were made of heart rate (HR), systolic blood pressure (SBP), mean blood pressure (BP), mean right atrial pressure (RAP), left ventricular end-diastolic pressure (PLVed), mean pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCP). The calculated haemodynamic parameters were:

$$\text{pulmonary arteriolar resistance (PAR)} = \frac{\text{PAP}-\text{PCP}}{\text{CO}} \cdot 80 \ (\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5})$$

$$\text{total peripheral resistance (TPR)} = \frac{\text{BP}-\text{RAP}}{\text{CO}} \cdot 80 \ (\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5})$$

After a control measurement, 25 mg urapidil was given i.v. and the measurements were repeated after 5 min. After 15 min a second dose of 25 mg urapidil was then given i.v. and the measurements were repeated after 20 and 45 min. Blood samples were taken for assay of plasma urapidil 5, 20, and 45 min after the first administration of the drug.

All data were analysed by the two-sided Wilcoxon-Pratt-Test; $p=0.05$ was taken at the lowest significance level.

Results

The acute haemodynamic effects of urapidil 5 min after the first and second doses of 25 mg i.v. and 45 min after the first injection are summarized in Table 2. The baseline haemodynamic measurements indicated severe congestive heart failure with increases in mean pulmonary artery (33.8±11.3 mm Hg) and capillary wedge pressures (24.9±10.8 mm Hg), and left ventricular end-diastolic pressure (31.2±9.4 mm Hg), and decreased cardiac output (4.59±0.67 l/min).

In all patients baseline systolic and mean blood pressure was in the normal range. After the first dose of 25 mg urapidil there was a significant decrease in systolic and mean blood pressure. The second dose of 25 mg urapidil led to a further pronounced fall to 94.9±14.6 and 77.3±11.4 mm Hg at 45 min, respectively, without symtoms of hypotension. There was no significant change in heart rate.

After 25 mg urapidil i.v. LV end-diastolic pressure decreased significantly, by about 30% from 31.2 ± 9.4 to 21.5 ± 8.3 mm Hg. The second dose of 25 mg led to a small further decrease to 19.3 ± 7.8 mm Hg at 45 min, i.e. to −38% of the baseline value. Mean right atrial pressure decreased from 5.9 ± 3.1 to 3.5 ± 2.1 mm Hg, i.e. by about −40% ($p < 0.05$).

Mean pulmonary artery pressure declined significantly from 33.8 ± 11.3 to 26.0 ± 10.2 mm Hg 5 min after 25 mg urapidil i.v. The second dose of 25 mg produced only a further small decrease to 23.3 ± 8.4 mm Hg at 45 min (−31% of the control value). Mean pulmonary capillary wedge pressure showed a decrease of −35% after 25 mg urapidil (from 24.9 ± 10.8 to 16.3 ± 7.4 mm Hg). The second dose of urapidil did not produce any further important change in pulmonary wedge pressure.

After 25 mg urapidil i.v. cardiac output increased significantly, by 15% from 4.59 ± 0.67 to 5.27 ± 1.05 $l \cdot min^{-1}$ ($p < 0.05$). The second dose of 25 mg urapidil led to a further increase in cardiac output to a mean of 5.58 ± 1.11 $l \cdot min^{-1}$ (+22%).

Pulmonary and peripheral resistances were calculated from these data. There was no significant change in pulmonary arteriolar resistance after urapidil, and all mean values were in the normal range. In contrast, total peripheral resistance fell from the slightly elevated control value of 1510 ± 242 to 1255 ± 302 $dyn \cdot s \cdot cm^{-5}$ (−17%; $p < 0.05$) 5 min after the i.v. injection. The second dose of 25 mg urapidil led only to a small, but significant further decrease in total peripheral resistance to −25% at 45 min.

Plasma urapidil concentrations at 5, 20 and 45 min were 0.647 ± 0.371, 1.135 ± 0.648 and 0.766 ± 0.332 $\mu g \cdot ml^{-1}$, respectively. All the patients tolerated the acute testing without side effects. They remained asymptomatic even during the reduction in arterial pressure.

Discussion

In patients with left ventricular failure there is an increase in peripheral vascular resistance. The reduced cardiac output leads to activation of the renin-angiotensin system and to sympathetic overactivity. Both these responses lead to further increases in vascular resistance and sodium and water retention, which tends to impair left ventricular function.

During the past decade vasodilators have been developed, which have proved a major advance in the treatment of patients with congestive heart failure, by reducing vascular resistance and so improving left ventricular performance. Vasodilators act primarily either on afterload, e.g. hydralazine [7] and nifedipine [8], or on preload, e.g. nitrates [9], angiotensin converting enzyme inhibitors [10], and sodium nitroprusside [11] reduces both pre- and afterload.

The purpose of the present study was to evaluate the acute haemodynamic effects of urapidil, a new antihypertensive drug with alpha-adrenoceptor blocking activity, in patients with severe congestive heart failure. All patients showed a reduction in pulmonary artery and wedge pressures and left ventricular end-diastolic pressure, as well as in arterial blood pressure and total peripheral resistance, which shows that urapidil reduces both arterial and venous tone. The concomitant increase in cardiac output without a significant rise in heart rate suggests an improvement in left ventricular performance.

The time course of the haemodynamic changes after the two doses of 25 mg urapidil shows that pronounced effects occurred within 5 min of the first i.v. injection.

The results are in good agreement with the findings of others, who have also examined the acute effects of i.v. urapidil in patients with chronic left heart failure [12, 13].

Thus, in patients with chronic left ventricular failure urapidil leads to a substantial reduction in left ventricular filling pressure by pre- and afterload reduction, with only moderate changes in blood pressure. There was a moderate increase in cardiac output in association with the reduced peripheral resistance. There was no significant change in heart rate. Urapidil produces acute haemodynamic effects in patients with congestive heart failure, which makes it a candidate for further, controlled therapeutic studies in heart failure.

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