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Urapidil therapy for acute hypertensive crises in infants and children

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Abstract. In 19 infants and children with acute and severe hypertension following a cardiovascular operation urapidil infusion was started for treatment of the hypertensive crisis. In all patients blood pressure was effectively reduced within 15 min. The drop in systemic blood pressure was combined with a reduction of central venous pressure. Heart rate and urine volume remained unaltered. Serum electrolytes after 12–24 h therapy showed a slight but significant decrease in serum sodium and an increase in serum potassium concentration. In one case urapidil treatment had to be interrupted because of hypotension. In this case the urapidil therapy was tolerated later in lower doses. Serious side effects were not observed. In our experience urapidil can be recommended for the treatment of hypertensive crises in children.

Key words: Acute hypertension – Urapidil – Children – Central venous pressure – Serum electrolytes

Introduction

Paradoxical hypertension after surgical resection of coarctation of the aorta is a well recognised phenomenon [8–10]. A hypertensive crisis can also occur after ligation of the ductus arteriosus and after resection of a subvalvular aortic stenosis. Severe hypertension after operation can have cerebral, cardiac and renal complications and may even lead to death. Anti-hypertensive treatment in these situations should be rapidly effective and without side effects. Several studies in the adult have proved the efficacy and safety of urapidil in acute hypertension [5, 14, 15, 18] as well as in therapy of chronic hypertension [3, 4, 7, 11, 16].

The purpose of this study was to evaluate the anti-hypertensive action of urapidil in infants and children and to give dose recommendations for the management of acute hypertensive crises after cardiovascular operations.

Patients and methods

During the period from January 1st 1983 to November 15th 1983, 19 infants and children in the intensive care unit of the pediatric department of the German Heart Centre, Munich, were treated with urapidil[a]. The patients, whose clinical characteristics are summarised in Table 1, were 14 males and 5 females. The mean age was 7.2 years (range 12 days to 14 years). Four patients were in the 1st year of life.

All children were in the early postoperative period: 16 patients had had a resection of coarctation of the aorta, one a ligation of the ductus arteriosus, one a total correction of an interrupted aortic arch, and one a resection of a subvalvular aortic stenosis. The indication for urapidil therapy was an acute hypertensive crisis in the immediate postoperative period with a duration of more than 1 h.

Arterial blood pressure measurements were done by an indwelling radial arterial catheter (22 gauge teflon catheter). Central venous pressure was obtained from a central venous catheter. For both arterial and central venous pressure monitoring a Gould Statham transducer (P23Db) was used. The data were presented continuously digitally by a Siemens monitor (Sirecust 310-NF4).

Routinely arterial and central venous lines, as well as an indwelling bladder catheter, were placed for intra- and postoperative monitoring. As a postoperative routine, patients received 1000 ml/m^2 5%–10% glucose solution, 20–40 mmol/m^2 potassium, and 20–40 mmol/m^2 sodium infusion daily.

Serum electrolyte determinations were done by flame photometry and by ion-selective electrodes (AVL Electrolyte Analyzer 980). In all patients the drug was administered by a continuous central venous infusion.

Two children came from the operating room with an infusion of nitroprusside-sodium (case 12) and clonidine (case 17). In both cases the anti-hypertensive therapy seemed insufficient and was replaced by urapidil. No other hypotensive drugs were applied during the infusion of urapidil.

In Table 2 the duration and the doses of urapidil therapy are presented. The mean duration of the infusion was 34 h (range 1–95 h). The initial infusion rate was 3.5 mg/kg per h (range 1–14). In all children except two, the initial dose coincided with the maximal dose. The mean maintenance dose was 1.1 mg/kg per h (range 0.2–3.3). In one patient two courses of treatment were applied with an interval of more than 24 h. The two courses (case 3 and 3a) are presented separately therefore in the statistics.

Regarding the doses in infants under 1 year of age (case 1–4) separately, it is important to note that in this young age group smaller doses of urapidil were administered: the initial dose was 2.1 mg/kg per h, the maintenance dose 0.8 mg/kg per h (Table 2).

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Abbreviations: SAP = systolic arterial pressure; MAP = mean arterial pressure; DAP = diastolic arterial pressure

[a] Ebrantil: Byk Gulden Pharmazeutika, Konstanz, FRG

Table 1. Clinical data and arterial blood pressures before treatment with urapidil

Patients	Sex	Age	Weight (kg)	Height (cm)	Diagnosis	Operation	Blood pressure (mmHg)		
							SAP	MAP	DAP
1	F	12 d	2.8	47	CoA, PDA	Resection, ligation, anastomosis	138	112	92
2	M	2 m	4.3	62	IAA	Correction	170	99	60
3	M	2 m	2.4	47	CoA, PDA	Resection, ligation, anastomosis	170	112	90
4	M	11 m	8.5	74	CoA	Resection, anastomosis	145	97	80
5	M	2 y	11	83	CoA	Resection, anastomosis	183	110	90
6	F	2 y	11	90	PDA	Ligation	160	99	80
7	F	3 y	9.8	83	CoA	Resection, anastomosis	150	112	80
8	M	6 y	17.3	116	CoA	Resection, anastomosis	160	106	80
9	M	8 y	26.2	126	CoA	Resection, anastomosis	180	112	90
10	M	8 y	23.7	127	Sub. AoS	Incision subv. membrane	200	102	73
11	M	8 y	21.7	118	CoA	Resection, anastomosis	160	109	82
12	M	10 y	44	134	CoA	Resection, anastomosis	224	114	85
13	F	11 y	21	115	CoA	Resection, anastomosis	200	107	70
14	M	11 y	38.3	130	CoA	Resection, anastomosis	190	106	70
15	M	13 y	29	138	CoA	Resection, anastomosis	225	100	72
16	M	14 y	41	160	CoA	Resection, anastomosis	205	108	60
17	M	14 y	36.7	143	CoA	Resection, anastomosis	250	174	150
18	M	14 y	69	177	CoA	Resection, anastomosis	158	107	95
19	F	14 y	35	152	CoA	Resection, anastomosis	232	132	95

Abbreviations: CoA = Coarctation of the aorta; PDA = persistent ductus arteriosus; IAA =interruption of the aortic arch; Subv.AS = subvalvular aortic stenosis; SAP = systolic arterial pressure; MAP = mean arterial pressure; DAP = diastolic arterial pressure

Table 2. Duration and doses of urapidil therapy

Patients	Duration of urapidil infusion	Dose		
		Initial (mg/kg per h)	Maintenance (mg/kg per h)	Total (mg)
1	83	1.8	0.9	198
2	47	1.0	0.3	59
3	4	1.9	1.1	11
3a	36	1.9	0.7	57
4	42	4.0	0.9	340
5	18	13.6	3.3	648
6	41	1.4	1.0	454
7	45	1.5	1.0	464
8	10	2.3	0.7	127
9	34	4.0	0.2	191
10	20	4.0	0.8	377
11	18	4.0	1.1	438
12	80	4.0	0.8	2764
13	1	4.0	2.0	42
14	28	1.9	0.7	785
15	16	4.0	1.0	481
16	95	3.6	0.6	2366
17	19	4.0	2.0	1413
18	3	4.0	1.8	371
19	43	4.0	1.1	1665
$\bar{x}$ (1–19)	34	3.5	1.1	647
$\bar{x}$ (1– 4)	42	2.1	0.8	133

In all cases the maintenance dose was adjusted according to the level of blood pressure. In 13 cases after therapy of the hypertensive crisis with urapidil infusion and stabilisation of blood pressure within safe limits no further anti-hypertensive drugs were necessary. In six cases after management of the hypertensive crisis persistent hypertension was treated orally by clonidine (three cases), urapidil (two cases), and nadolol (one case).

The results were analysed using standard statistical methods, and for significance the paired Student-*t*-test was applied.

Results

Blood pressure

The circulatory effects of urapidil on systolic arterial pressure (SAP), mean arterial pressure (MAP), and diastolic arterial pressure (DAP) are presented in Table 3. With the start of the urapidil infusion there was an immediate and persistent decrease in SAP, MAP, and DAP. During the whole monitoring period the decrease in blood pressure was in the range of 16%–26%. Systolic and diastolic blood pressure were equally influenced.

Figure 1 illustrates the mean doses of urapidil during the first 12 h infusion and the corresponding changes in arterial pressure. The initial urapidil infusion rate of 3.4 mg/kg per h seems sufficient to overcome the hypertensive crisis. During 1 h the infusion rate can be reduced to 1.1 mg/kg per h with small variations in the following hours. No significant re-

Table 3. Mean absolute value (X) and standard deviation (SD) of blood pressure before and during the first 12 h of urapidil therapy. %d = mean of each percentage decrease (X and SD) during urapidil therapy

Time (h)	*n*	SAP				MAP				DAP			
		mmHg		%d		mmHg		%d		mmHg		%d	
		X	SD	X	SD	X	SD	X	SD	X	SD	X	SD
–1.00[a]	18	170	34	—	—	105	11.7	—	—	81	34.8	—	—
0[a]	20	180	35.1	—	—	110	17.1	—	—	83	18.7	—	—
0.25	20	145	29.2	18.3	13.1	88	11.2	19.1	13.3	66	11.6	18.8	16.3
0.5	20	140	32.6	21.3	13.6	84	12.7	22.5	14.3	63	11.6	23.1	18.1
0.75	20	138	34.1	22.8	14.1	83	11.2	23.7	13.5	62	11	23.8	15.3
1.00	20	141	31.9	21.3	11.8	82	9.1	24.6	12.8	64	12.6	22.3	13.8
1.25	19	143	33.1	19.8	11.3	84	8.8	23.2	10.3	62	8.9	24	13.6
1.5	19	142	30	20.5	9.5	83	6.6	22.8	11.7	62	7.9	24	13.7
1.75	19	140	29.9	21	9.9	84	6.3	22.1	11.9	61	7.2	24.4	12.8
2.00	19	139	31.2	21.7	11.9	82	7.9	24.2	11.9	60	8.5	26.4	13
3.00	19	138	29.7	21.8	13.3	84	6.6	22.1	11.9	62	7.1	24.2	14.2
4.00	18	142	31.8	20.7	12.2	85	8.9	22	14.1	64	9	20.4	13.1
5.00	17	146	27.2	20.1	10.9	88	8.3	19.3	12.4	64	8.7	22.2	14.9
6.00	16	148	24.7	19	10.9	89	8.2	18.9	12.3	66	8.4	19.2	15.3
7.00	16	142	40	17.4	10.2	89	8.9	17.5	13.1	67	7.1	19.2	12.9
8.00	16	151	27.3	15.5	10.4	89	8.8	18.9	12.7	68	7.4	17.5	17.4
9.00	16	148	32.4	18	10.9	90	11.9	17.8	14.7	68	9.9	17.5	17.4
10.00	16	150	27.7	17.4	8.4	86	7.6	21.4	11	66	6.5	19.7	11.8
11.00	16	139	40.2	18.4	9.3	87	8.6	20.4	12	67	7.3	17.6	14.3
12.00	16	146	26.9	19.4	8	87	7.3	20.8	10.3	66	6.6	19.4	12.4

[a] Before the infusion of urapidil

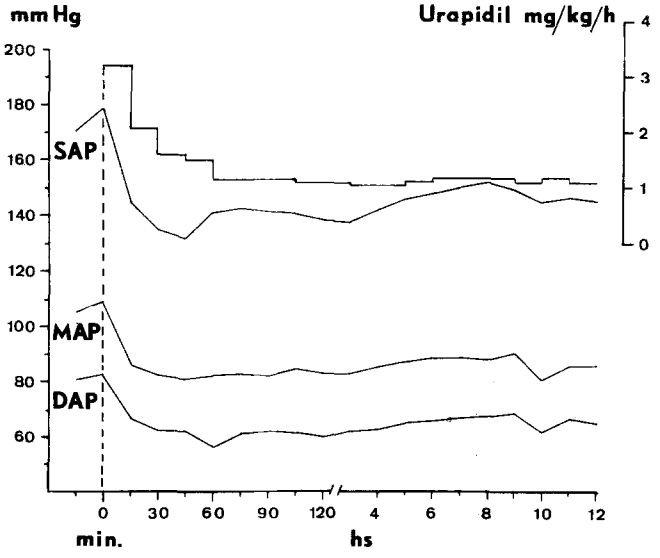

Fig. 1. Mean dosage of urapidil and mean response of arterial blood pressure during the first 12 h of therapy in 19 infants and children (Abbreviations, see Table 1)

increase of urapidil therapy in that phase was necessary. After the discontinuation of urapidil infusion a new dramatic increase in the arterial blood pressure was not observed.

Heart rate and central venous pressure

There was a tendency to a slightly diminished heart rate, but without any significance (Tables 4 and 5). The central venous

Table 4. Heart rate (HR) and central venous pressure (CVP) before and during the first 12 h of urapidil infusion

Time (h)	*n*	HR (b/m)	*n*	CVP (mmHg)
–1	20	122	11	5.3
0	20	132	15	5.3
0.25	20	129	14	4.3
0.5	20	129	15	4.3
0.75	20	131	15	3.1
1.00	20	127	15	3.5
1.25	19	129	12	3.4
1.5	19	129	13	3.9
1.75	19	129	13	3.5
2.00	19	129	14	4.1
3.00	19	127	11	3.2
4.00	18	129	13	3.7
5.00	17	127	12	3.5
6.00	16	129	11	3.7
7.00	16	130	11	3.8
8.00	16	129	11	3.6
9.00	16	129	11	2.6
10.00	15	125	11	2.7
11.00	15	125	11	3.0
12.00	15	122	11	3.6

Table 5. Significance (*P*-values) of changes in blood pressure, heart rate, and central venous pressure during the 1st h of urapidil infusion. (For abbreviations see Tables 1 and 4)

Time (min)		SAP	MAP	DAP	HR	CVP
15	*P*	<0.0005	<0.0005	<0.0025	ns	<0.005
30	*P*	<0.0005	<0.0005	<0.0005	ns	<0.05
45	*P*	<0.0005	<0.0005	<0.0005	ns	<0.025
60	*P*	<0.0005	<0.0005	<0.0005	ns	<0.05

Table 6. Urine output and diuretic therapy before and during urapidil infusion

Patients	Before the infusion of urapidil		During the infusion of urapidil	
	Furosemide (mg/kg per h)	Urine output (ml/kg per h)		Furosemide (mg/kg per h)
1	0.3	7.5	3.3	0.3
3	1.2	4.7	4.9	1.0
3a	0.7	3.2	4.3	0.5
4	—	3.0	1.7	0.01
5	—	2.0	2.7	—
8	0.03	1.9	2.0	0.03
9	—	1.3	0.8	—
11	—	2.1	2.2	0.02
15	—	2.0	1.8	—
18	—	1.3	1.6	—
19	—	1.3	1.5	—
$\bar{x}$	0.20	2.75	2.4	0.17
SD		1.9	1.3	
n	11	11	11	11

pressure showed a mean decrease in the range of 19%–51% (Tables 4 and 5).

Urine volume

Urine volume before and after urapidil therapy was compared in 11 patients. In the other patients a comparison was not possible because the period before urapidil therapy was too short. In addition the diuretic therapy before and after urapidil treatment was compared. According to Table 6 urine excretion was not changed by urapidil and also the applied doses of furosemide before and after urapidil treatment were not different.

Serum electrolytes

In the first 10 h of the urapidil infusion there was a slight tendency to a decrease in serum sodium and an increase in serum potassium but without statistical significance. During the second period of urapidil infusion (11–24 h) there was a significant increase in serum potassium and a slight but also significant decrease in serum sodium (Table 7).

Side effects

Side effects like nausea, giddiness, and headache were not observed. Only in one case was the hypotensive effect of urapidil in the first 5 min after the start of infusion so severe that it required interruption of the infusion (Fig. 2). The infusion could be restarted 75 min later at a lower dose. Also the maintenance dose in that case was smaller than normal.

Table 7. Changes in sodium and potassium serum levels during the first 24 h of urapidil infusion

Patients	Before the infusion of urapidil		During infusion of urapidil			
			1–10 h		11–24 h	
	Na^+	K^+	Na^+	K^+	Na^+	K^+
	(mmol/l)		(mmol/l)		(mmol/l)	
1	134	3.3	135	4.3	139	4.1
2	136	3.4	136	3.3	139	4.0
4	140	3.7	143	3.9	142	5.0
5	145	3.6	136	3.5	142	4.9
6	143	4.4	140	3.3	135	4.0
7	137	4.0	137	4.5	138	4.4
9	144	3.7	136	4.4	139	4.0
11	137	3.5	140	3.7	128	4.4
12	140	3.8	140	3.8	136	3.9
14	140	4.5	140	4.1	129	4.5
15	144	3.4	136	3.7	135	4.1
16	141	3.3	140	3.9	139	4.7
17	140	4.4	140	3.8	136	5.0
19	145	3.5	143	3.8	138	4.3
$\bar{x}$	140.4	3.8	138.6	3.9	136.8	4.4
SD	3.5	0.4	2.6	0.4	4.1	0.4
P	—	—	ns	ns	<0.01	<0.0005

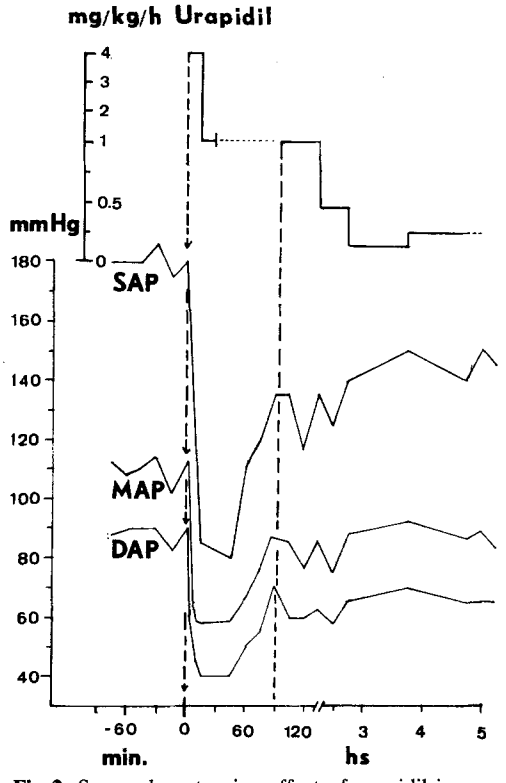

Fig. 2. Severe hypotensive effect of urapidil in one case 5 min after start of the infusion (Abbreviations, see Table 1)

Discussion

Previous investigators have demonstrated the anti-hypertensive action of urapidil in adult patients [5, 7, 11, 15, 16, 18]. This is the first study showing the clinical characteristics of urapidil therapy in infants and children.

In the absence of any experience of application of urapidil in children, we preferred the continuous venous infusion as the safest method of administration thus allowing a rapid adaptation of the infusion rate according to the decreased arterial blood pressure. Our initial infusion rate was in agreement with the doses applied in adult patients [1].

In our experience the following doses have been safe and effective: In children more than 6 years of age with SAP 150–200 mm Hg and MAP more than 100 mm Hg, the initial rate of infusaion should be 3 mg/kg per h (in most cases not longer than 15 min), followed by a maintenance dose of 1 mg/kg per h. If SAP is more than 200 mm Hg, an initial dose of 4 mg/kg per h is recommended.

In infants and young children up to 6 years of age an initial rate of 2 mg/kg per h and a maintenance dose of 0.8 mg/kg per h seems sufficient.

It remains essential however to emphasise, that especially in the first 30 min after the start of infusion the arterial pressure should be monitored continuously, if possible by direct arterial measurements. A severe hypotension can occur immediately after start of the infusion as shown in one of our cases (Fig. 2). It seems advisable to perform this therapy only within the confines of an intensive care unit.

It should be kept in mind, however, that the above recommended doses were applied only to children with hypertensive crises. With other indications, for example therapy of low cardiac output, urapidil should be applied at lower initial doses [12].

In all cases a prompt decrease in systolic, mean and diastolic blood pressure was achieved within the first 15 min of therapy and this effect lasted throughout the whole urapidil infusion. Concomitant was a decrease in central venous pressure without changes in heart rate. A slight decrease in central venous pressure was also observed in other studies [2, 13].

Our data in 19 children showed no alterations in diuresis, thus facilitating the use of urapidil in renal failure. In adult patients with renal failure urapidil therapy was tolerated well [18].

In clinical observations of other groups [5, 15, 18] no changes in electrolyte balance were reported. Our data indicate a slow increase in serum potassium and a decrease in serum sodium being significant only after at least 12 h of therapy. Before assuming that urapidil interferes with the action of aldosterone, we plan to compare our data with a control group without urapidil therapy.

The mechanism of action of urapidil combines two major principles according to present knowledge [6, 13, 17]:

1. reduction of vascular resistance because of inhibition of post-synaptic alpha$_1$-adrenoceptors;
2. avoidance of significant counter-regulation (e.g. heart rate, plasma renin activity) by modification of central sympathic tone and peripheral sympathetic neurotransmission.

From a pathophysiological point of view urapidil, which lowers peripheral vascular resistance without increasing heart rate, appears to be a favourable substance for anti-hypertensive therapy.

In conclusion, we confirm the prompt and rapid antihypertensive action of urapidil in infants and children. Short term therapy, at least, seems to be without any serious side effects.

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