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Urapidil permeates the intact blood-brain barrier

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Abstract. *Objective:* To determine the plasma and cerebrospinal fluid (CSF) levels of urapidil after i.v. administration and the effect on CSF serotonin and 5-hydroxyindoleacetic acid (5-HIAA) concentrations.
Design: Open, single-dose study.
Setting: Post-surgery following neurosurgical removal of the hypophysis ($n = 5$) or aneurysm clipping ($n = 1$).
Patients: 6 patients, aged 32–71 years, with intact blood-brain barrier (BBB); 1 patient was studied twice.
Interventions: Single dose of 25 mg urapidil i.v. as prophylaxis of BP increase during extubation or as treatment of hypertensive episodes.
Measurements and results: Urapidil, serotonin and 5-HIAA were measured by HPLC in CSF during 8 h after urapidil administration. Urapidil was detected in CSF as soon as 5 min after injection in 3 patients. The concentration ratio of plasma/CSF after the distribution phase was about 5:1. No significant effect on serotonin and 5-HIAA in CSF was seen.
Conclusion: After administration of a therapeutic dose, urapidil permeates the BBB and may interact with central 5-HT_{1A}-receptors.

Key words: Blood brain barrier – Urapidil – Serotonin-($5HT_{1A}$) – Receptors – Cerebrospinal fluid

Urapidil is a useful drug to prevent hypertensive peaks in patients with severe head injuries because the drug does not increase intracranial pressure [1]. Urapidil is a phenylpiperazine-substituted derivative of uracil and is a selective alpha$_1$-adrenoreceptor antagonist which decreases blood pressure by lowering peripheral resistance. Reflex tachycardia does not usually occur except for a slight transient increase in some cases immediately after bolus injection. It is assumed that the sympathetic counter-regulation is suppressed by an agonistic effect of urapidil on central serotonin-($5HT_{1A}$)-receptors located in the brain stem. Binding of urapidil to 5-HT_{1A}-receptors has been studied in animal models [2–4], but little is known about the urapidil binding capacity to serotonergic receptors in humans. The blood brain barrier passage of urapidil has been investigated in one study where urapidil was analyzed in cerebrospinal fluid in 9 patients in the presence of compromised intracranial dynamics [1]. So far, no data are available in patients with an intact blood brain barrier (BBB).

The objective of this study was to investigate 1) the lag time between urapidil administration and detection of urapidil in cerebrospinal fluid, 2) the time period during which urapidil was detectable in cerebrospinal fluid after intravenous injection, 3) the ratio of urapidil plasma concentration to urapidil cerebrospinal fluid concentration, and 4) the possible influence of urapidil on CSF serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations.

Methods

Six patients (3 men and 3 women, 32–71 years old) were studied in the course of this open study. One patient (no. 1) was studied on two occasions, separated by 13 days. Demographic data are shown in Table 1. Five patients were undergoing neurosurgical removal of the hypophysis with clinical necessity of an indwelling lumbar subarachnoid catheter. This catheter was placed at the end of operation to assure a drainage of CSF in case of an increase in intracranial pressure. The transspenoidal access to the hypophysis keeps the blood-brain barrier intact. One patient who underwent an aneurysm clipping 14 days prior to study with external drainage of the cerebrospinal fluid was included after measurement of the albumin/prealbumin quotient had shown that the BBB was intact (albumin 135 mg/l, prealbumin 15 mg/l, ratio ca. 9:1). He suffered from severe hypertension, and so he was administered 25 mg of urapidil to reduce a sudden increase in blood pressure. In 2 other cases, urapidil was given in the intensive care unit to reduce an elevated blood pressure. In 4 cases urapidil (25 mg) was administered before extubation to prevent a blood pressure rise.

The study was performed at the Department of Anaesthesia, University of the Saarland, Homburg, Germany

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Table 1. Demographic and anthropometric data of the patients

No	Age (years)	Sex	Weight kg	Height cm
1[a]	50	m	85	180
2	71	m	80	175
3	38	f	59	168
4	46	m	92	182
5	32	f	67	170
6	63	f	93	162

[a] Patient 1 was studied twice. The second investigation was repeated 13 days after the first one

CSF and EDTA-blood plasma samples were drawn at 0, 5, 10, 15, 20, 30 min and 1 h, 2 h, 3 h, 5 h and 8 h after initial urapidil administration intravenously. EDTA-plasma samples and CSF samples for urapidil analysis and CSF samples for albumin and prealbumin determination were centrifuged and stored at −18 °C. With the albumin concentration in the CSF the integrity of the blood brain barrier can be assessed. Normally the BBB is neither permeable for red blood cells nor for proteins like albumin. Therefore, an elevated CSF-albumin concentration indicates an impaired function of the BBB with an unphysiological increased permeability [5]. CSF samples for determination of serotonin and 5-HIAA were stored at −70 °C until analysis.

Urapidil was determined by HPLC at the Byk Gulden laboratories [6]. The following pharmacokinetic variables were derived: the elimination half-life in plasma t1/2, the area under the plasma concentration-time curve AUC from t = 0 until t = 8 h, the clearance CL, the volume of the central compartment V_1, and the volume of distribution at pseudo-steady-state Vd_{area}. The concentration of albumin and prealbumin in CSF were determined by electrophoresis and the concentrations of serotonin and 5-HIAA in CSF were determined by ion pair HPLC on a reversed phase column with electrochemical detection at 0.6 V. Coefficients of variations were between 5.4 and 7.5% for 5-HIAA and between 4.7 and 12.8% for serotonin. These analyses were performed at the Laboratory Clotten, Freiburg, Germany. CSF-samples for serotonin, 5-HIAA, prealbumin and albumin were not available in patient 6.

Since there was no control group the study was evaluated descriptively.

Results

Albumin concentrations in CSF

The CSF-albumin concentrations were within the normal range (180–260 mg/l, [5]) in most samples. Patient 3 had increased concentration up to 700 mg/l 40 min after administration. Also the concentrations of patient 5 were slightly increased (ca. 350 mg/l).

Urapidil concentration in CSF and plasma

Urapidil was detected in the CSF of all patients. The concentrations of urapidil measured in plasma and CSF are shown in Figs. 1 and 2. At 5 min after i.v. injection of urapidil, 3 patients had CSF urapidil concentrations in the range of 0.010–0.056 mg/l. In the other patients urapidil was detectable in CSF after 10 min (0.010–0.014 mg/l).

The maximum concentration of urapidil in the CSF (median 0.042 mg/l, range 0.023–0.175 mg/l) was reached 2 h (median, range 0.5–3 h) after i.v. administration (Fig. 2). Urapidil was detectable even after 8 h in the CSF of 5 patients. The median area under the concentration time curve (AUC_{0-8h}) of urapidil in CSF was 0.23 mg/l/h (Range: 0.15–0.81 mg/l/h).

Table 2. Pharmacokinetic parameters of urapidil in plasma and CSF after single i.v. administration of 25 mg

	Plasma			CSF		
	Median	Min	Max	Median	Min	Max
t 1/2 [h]	2.4	1.9	3.5			
AUC [mg/l/h][a]	2.83	1.45	4.80	0.23	0.15	0.81
Cl [l/h]	8.83	5.21	7.25			
Vd_{area}[l]	30.8	18.6	57.0			
V_1 [l]	11.60	3.52	19.83			

[a] AUC from 0–8 h after administration
The following equations were used:
Cl = D/AUC; V1 = D/C_0; Vd_{area} = Cl/β (where D = dose; C_0 = plasma concentration at t = 0 h; β = terminal elimination constant)

The median maximum concentration of urapidil in plasma was 1.445 mg/l (range 0.958–3.758 mg/ml) after 5 min. The median AUC_{0-8h} of urapidil in plasma was 2.83 mg/l/h (range 1.45–4.80 mg/l/h). Thus, the ratio of median AUCs (CSF/plasma) was 8.1%.

After termination of the distribution phase a ratio of urapidil plasma-concentration to CSF-concentration was estimated to be approximately 5 : 1.

The calculated pharmacokinetic parameters of urapidil are given in Table 2. A reliable estimation of the elimination phase and consequently the half-life in CSF was not possible, since the observation period was too short.

Serotonin and 5-HIAA concentrations in CSF

After a slight increase in some patients, serotonin CSF levels tended to decline during the observation period. 5-HIAA concentrations remained more or less unchanged (Table 3). Both serotonin and 5-HIAA levels showed great interindividual variations. No adverse events were observed.

Table 3. Concentrations of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) at different time points in 6 patients

Time (h)	5-HT (µg/l)			5-HIAA (µg/l)		
	Median	Min	Max	Median	Min	Max
0.00	1.02	0.72	1.62	94.1	19.4	144.5
0.08	1.00	0.77	1.58	106.8	28.0	152.1
0.17	1.02	0.81	1.73	99.9	37.7	136.8
0.25	1.08	0.77	1.42	106.4	34.5	150.2
0.33	1.08	0.75	1.38	96.4	32.4	149.3
0.5	0.99	0.78	1.41	96.3	34.5	132.5
1	1.04	0.61	1.37	91.9	19.5	149.3
2	0.91	0.58	1.29	91.5	15.1	128.5
3	0.90	0.63	1.30	92.4	30.2	133.5
5	0.89	0.62	1.25	96.0	31.2	120.5
8	0.82	0.68	1.32	91.2	25.8	134.1

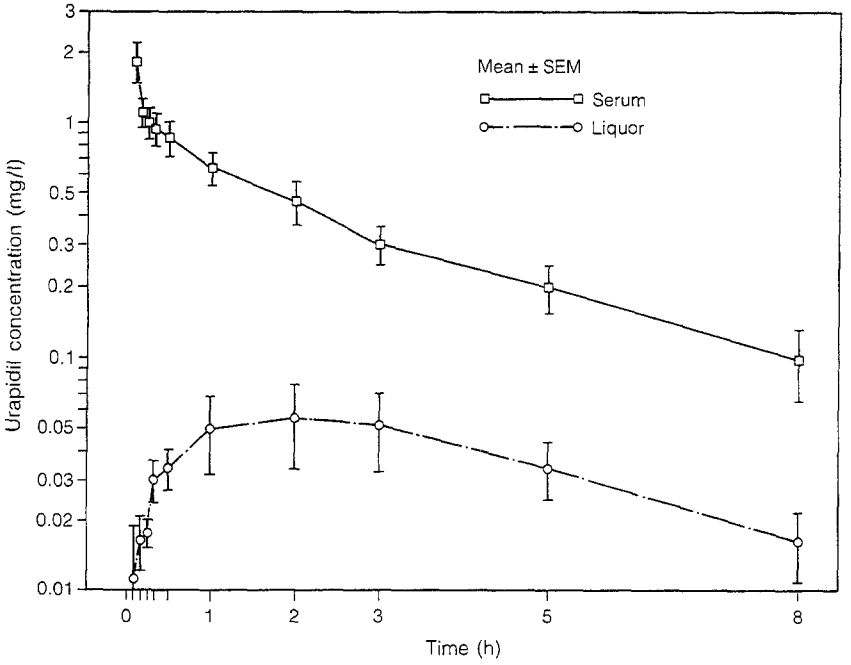

Fig. 1. Urapidil concentrations (mean ± SEM) in plasma and in cerebrospinal fluid after intravenous injection of 25 mg or urapidil ($n = 7$)

Discussion

The present study demonstrates that urapidil does penetrate the intact BBB and can be detected in the CSF as soon as 5 min after administration. There is increasing evidence that $5HT_{1A}$ receptor stimulation is responsible for a central effect of urapidil [2, 3], which contributes to the decrease of blood pressure mediated via the postsynaptic vascular $alpha_1$-adrenoreceptor blockade. The site of action in the brain is located in the ventral part of the medulla oblongata, exactly in the intermediate chemosensitive zone of the ventral medullary surface and the lateral reticular nucleus, which was proven by topical application [4].

The measurement of serotonin and 5-HIAA, which may represent the discharge of serotonergic neurons showed no definite trend. Serotonin is not able to cross the BBB [7] and is primarily converted to 5-hydroxyindoleacetic acid (5-HIAA). Thus, 5-HIAA measured in the CSF should reflect the central serotonin turnover. However, the interpretation of lumbar CSF 5-HIAA is very difficult [8], since approximately 50% of lumbar CSF 5-HIAA is derived from spinal cord. In addition, there is a ventriculo-lumbar gradient for 5-HIAA. Only one third of the 5-HIAA produced in the brain enters the CSF, while an uncontrollable amount is transferred directly into the bloodstream [8]. Production and turnover of CSF is very rapid with the total volume being renewed

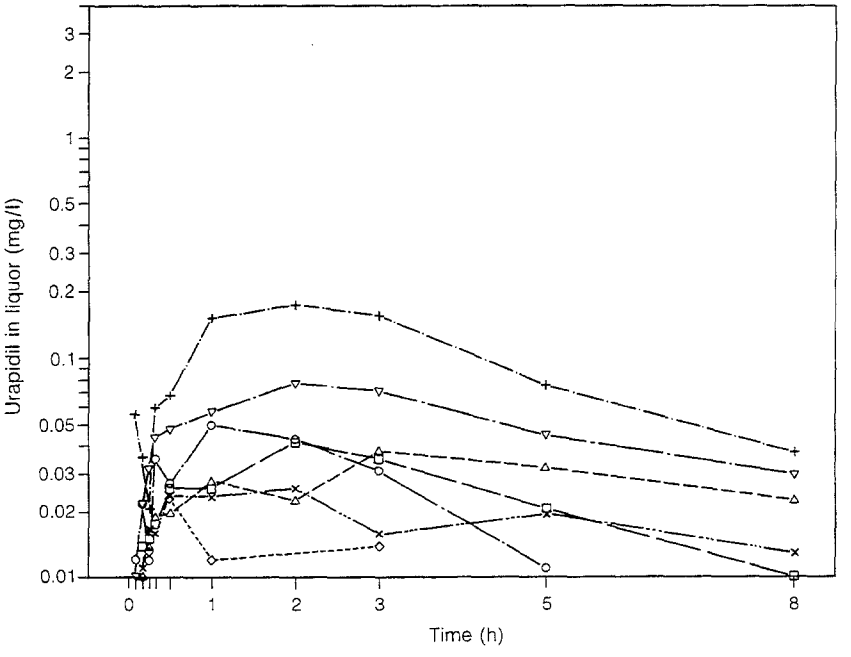

Fig. 2. Concentrations of urapidil in cerebrospinal fluid of the individual patients after i.v. injection of 25 mg urapidil

every 5–7 h. Since no control group without urapidil administration was investigated, no interpretation of the data is feasible. However, the data are listed because information about CSF 5-HIAA is very rare and divergent in literature [9–11]. Differences in absolute values are certainly caused by different analytical methods, sampling and storing conditions of the samples.

Although it is not known in humans to which extent urapidil may enter brain tissues to interact with ($5HT_{1A}$-receptors, the presence of urapidil in CSF may be considered as prerequisite for an additional central mode of action. Since the binding affinity of urapidil for ($5HT_{1A}$)-receptors in the brain is 10 times higher than for $alpha_1$-adrenoceptors [12] much lower concentrations in the CNS than in the systemic circulation may be sufficient to cause pharmacological effects.

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