Permeation of the blood–brain barrier by urapidil and its influence on intracranial pressure in man in the presence of compromised intracranial dynamics

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We studied eight patients undergoing craniotomy for intracerebral tumour surgery requiring monitoring of intracranial pressure. All these patients showed significantly increased systolic arterial pressure, during anaesthesia. Following an average dose of 0.8 ± 0.22 mg/kg urapidil, systolic arterial pressure returned to baseline values without a significant change in intracranial pressure.

In nine patients, urapidil concentrations in plasma and cerebrospinal fluid were assayed following an intravenous injection of urapidil. Urapidil was found in the cerebrospinal fluid in concentrations between 5 and 99 ng/ml after total cumulative bolus injections of 10–75 mg. There is evidence that in clinically applied doses urapidil permeates the blood–brain barrier and reaches cerebrospinal fluid concentrations that allow an interaction with central 5-hydroxytryptamine-1A receptors.

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Introduction

Most antihypertensive drugs, in particular direct vasodilators, like nitroglycerin, sodium nitroprusside, hydralazine and diazoxide increase intracranial pressure by increasing cerebral blood volume [1–4]. Cerebral vasodilation is a potential hazard when intracranial pressure is increased or when intracranial compliance is impaired, with impending cerebral ischaemia as long as the skull remains closed [1–3].

The antihypertensive mechanism of urapidil has been attributed both to postsynaptic vascular α-adrenoceptor blockade and to a reduction in central sympathetic discharge [5–7]. In contrast to other vasodilators, with urapidil the decrease in arterial pressure is not accompanied by a reflex increase in sympathetic nerve activity or the heart rate [7–9]. Increasing evidence indicates that 5-hydroxytryptamine is involved in the central control of cardiovascular function [3,6].

Patients and methods

Eight patients (study 1) and nine patients (study 2) undergoing craniotomy for intracranial tumour surgery were studied. Immediately following induction of neuroleptanaesthesia an intraventricular catheter was placed via a burrhole and intracranial pressure was recorded continuously. When hypertensive reactions occurred that did not respond to fentanyl, urapidil was administered intravenously according to clinical requirements. Systolic, diastolic and mean arterial pressure, the heart rate and intracranial pressure were recorded. Data are expressed as means ± s.d. and statistical analysis was carried out with Student's t-test, taking $P < 0.05$ statistically significant.

Plasma and cerebrospinal fluid concentrations of urapidil and of albumin, prealbumin and haemoglobin were assayed in nine patients undergoing craniotomy for cerebral tumour surgery, requiring external drainage of cerebrospinal fluid from the intraventicular cavity.

Results

All patients studied exhibited hypertensive events in spite of repeated fentanyl bolus injections. The overall dose of urapidil required to treat these intra-operative hypertensive episodes, calculated on an average dose per kg body weight basis, was 0.8 ± 0.22 mg/kg. All patients ex-

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perienced significant hypertensive reactions during the conduct of anaesthesia (Table 1). Following the administration of urapidil, systolic arterial pressure decreased to baseline values, without a significant change in intracranial pressure (Table 1). The heart rate remained unchanged.

After intravenous bolus injections of 10–35 mg, urapidil and its metabolite were detected in the cerebrospinal fluid of all nine patients. Following the administration of 10–75 mg (maximum cumulative dosage), urapidil was assayed in cerebrospinal fluid in concentrations of 5–99 ng/ml which is the equivalent of 5–10% of the plasma urapidil concentrations (range 100–4400 g/ml). The haemoglobin blood to cerebrospinal fluid ratio was 16 to 748 times higher than the corresponding urapidil plasma to cerebrospinal fluid ratio, thus ruling out contamination with blood as a major source of the urapidil concentrations in cerebrospinal fluid. Elevated cerebrospinal fluid albumin and blood–brain barrier-dependent prealbumin concentrations were found in eight out of the nine patients, implying an impaired blood–brain barrier in these eight. The cerebrospinal fluid concentration of urapidil in the patient with the intact blood–brain barrier was in the same range as in the other eight patients. The cerebrospinal fluid concentration of urapidil increased slightly, reaching a maximum 120 min (110 nmol/l) after a bolus injection of 30 mg.

Discussion

In animal studies urapidil does not increase intracranial pressure nor cerebral blood flow, as determined by the injection of radioactive markers in the carotid artery [10,11]. These findings similarly apply to humans as shown by our results. In the present study urapidil decreased arterial pressure to control values, as measured in the awake state, without a rise in intracranial pressure in spite of intracranial space-occupying lesions and pre-existing elevated intracranial pressure values.

The antihypertensive mechanism of urapidil has been attributed both to peripheral postsynaptic α_1-adrenoceptor blocking properties and to a reduction in central sympathetic nerve activity. Radioligand binding studies have revealed a high affinity of urapidil for central nervous system 5-hydroxytryptamine-1A receptors; this affinity is highly selective since it discriminates between 5-hydroxytryptamine-1B receptors and 5-hydroxytryptamine-2 receptors [3,6].

Injection of urapidil into the fourth ventricle decreased arterial pressure [8]. Topical application of urapidil to the ventral medullary surface also decreased arterial pressure [5]. Topical application of high doses of urapidil to the ventral surface of the medulla oblongata produced a reduction in preganglionic sympathetic nerve activity [9] as high intravenous doses do [5,8].

Our results show that urapidil is able to permeate the intact blood–brain barrier in humans. The intravenous injection of urapidil in a dose currently used in the clinical setting revealed cerebrospinal concentrations of up to 100 nmol/l. At this concentration cardiovascular changes by interaction with central nervous 5-hydroxytryptamine-1A receptors were found in animal experiments.

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Table 1. Haemodynamic parameters in eight patients undergoing craniotomy.

	Baseline (awake)	Before urapidil	Following urapidil		
			5 min	10 min	20 min
Systolic arterial pressure (mmHg)	130.6 ± 10.8	162.5 ± 16.9*	130 ± 14.4	130 ± 10.8	123 ± 20.5
Diastolic arterial pressure (mmHg)	73 ± 7.4	77 ± 10	76 ± 8	72.5 ± 9.6	68.7 ± 12
Mean arterial pressure (mmHg)	93 ± 7.5	108 ± 12*	93.5 ± 9.2	90.2 ± 10.6	87 ± 14.2
Heart rate (beats/min)	81 ± 8	80 ± 7	83 ± 8	77 ± 10	77 ± 7
Intracranial pressure (mmHg)		15.2 ± 4.7	14.8 ± 3.9	14.4 ± 3.2	14.8 ± 3.8

*$P < 0.05$ compared with baseline.