The Effects of Verapamil on Cerebrospinal Fluid Pressure in Surgical Patients

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The effects of verapamil upon cerebrospinal fluid pressure (CSFP) were studied in twenty surgical patients without intracranial pathology who were divided into two groups of ten patients each: verapamil 0.075 $mg \cdot kg^{-1}$ was given in group 1 and 0.15 $mg \cdot kg^{-1}$ was given in group 2. A spinal needle was inserted into the subarachnoid space to permit continuous measurement of CSFP. Intravenous verapamil as a bolus produced a statistically significant increase in CSFP: from 6.0±3.5 (mean±SD) to 10.5±4.3 mmHg in group 1 ($P < 0.01$), and from 6.2±3.1 to 12.6±3.8 mmHg in group 2 ($P < 0.01$). CSFP after verapamil attained its maximum in 0.5–1.5 min, then gradually returned to control levels. Changes in CSFP were always associated with statistically significant decreases in arterial blood pressure and cerebral perfusion pressure, while the heart rate showed variable changes. It is concluded that a clinical dose of verapamil showed variable changes. It is concluded that a clinical dose of verapamil (0.075–0.15 $mg \cdot kg^{-1}$) has no neurological side effects in patients without intracranial hypertension. However, it must be emphasized that verapamil may increase CSFP to undesirable levels and should be avoided in patients with compromised intracranial compliance. (Key words: cerebrospinal fluid pressure, calcium entry blocker, verapamil)

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Verapamil, a calcium entry blocker, is currently used to manage several cerebro- and cardiovascular disorders, including cerebral or coronary vasospasms[1–3], hypertension[4], and supraventricular tachyarrhythmias[5–8]. Recently calcium entry blockers, administered before or after the ischemic insult, have been suggested to ameliorate the brain damage and improve the neurologic outcome in animal experiments[9–11]. Hence, they are of great promise in cerebral resuscitation. On the other hand, they have been reported to elevate intracranial pressure (ICP) in animals with or without intracranial hypertension[12,13]. Clinical observations by Bedford and his colleagues[14] have pointed out an adverse effect of verapamil upon ICP in patients with brain tumors. The authors reported previously that changes in cerebrospinal fluid pressure (CSFP) after nicardipine has little neurological side effects in normal patients[15]. The present investigation was designed to evaluate the effects of verapamil on CSFP in surgical patients without intracranial lesions in an attempt to estimate its safety in ordinary clinical practice.

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Methods

The study protocol was approved by the Institutional Human Studies Committee of Sapporo Medical College, and informed consent was obtained from each patient. Twenty adult patients (15 women, 5 men), ranging in age from 22 to 69 yr, who were scheduled to have spinal anesthesia for their

surgical procedure, were selected for this study. No patient had any neurological or cardiopulmonary disorders. Premedications consisted of an intramuscular injection of hydroxyzine, 100 mg, and atropine, 0.5 mg, 1 hr before arrival in the operating room. A 16-gauge intravenous catheter was placed for infusion of lactated Ringer's solution at a rate of 5 $ml \cdot kg^{-1} \cdot 15\ min^{-1}$ and for drug administration. A 20-gauge catheter was inserted into the radial artery under local anesthesia for continuous measurement of arterial blood pressure (AP) and for sampling arterial blood. After sterilizing the lumbar region, the patient lying in the lateral position, a 22-gauge spinal needle was introduced into the space between the third and fourth lumbar vertebrae. Upon demonstration of the free flow of clear cerebrospinal fluid, the needle was connected with a low compliance catheter to a transducer for continuous measurement of CSFP. The inside of the catheter was filled with sterile normal saline solution so as not to remove cerebrospinal fluid, and care was taken to avoid introduction of air bubbles into the line. All pressures were continuously transduced (Statham P23ID transducer, Gould, USA) and recorded on a polygraph system (San-Ei, Tokyo) with the zero reference point at the midline of the vertebral column.

Patients were randomly assigned to one of the following two groups according to the dosage of verapamil, group 1 ($0.075\ mg \cdot kg^{-1}$, n=10), group 2 ($0.15\ mg \cdot kg^{-1}$, n=10). After a period of stable CSFP, AP, and HR was observed, verapamil was given intravenously over 5 sec. CSFP, ECG, AP, and HR were continuously recorded for 15 min. Arterial blood samples were obtained before and 15 min after the injection of verapamil for measurement of pHa, $Paco_2$, Pao_2, and BE by Acid Base Laboratory 3 (Radiometer, Copenhagen). Mean arterial blood pressure (MAP) was calculated as diastolic blood pressure plus one-third the pulse pressure, and mean CSFP was calculated as diastolic CSFP plus one-half the intraspinal pulse pressure. Cerebral perfusion pressure (CPP) was calculated from the difference between MAP and mean CSFP.

Table 1. Patient characteristics and arterial blood gas tensions before and after verapamil

		Group 1	Group 2
Number of patients		10	10
Sex (female/male)		7/3	8/2
Dose of verapamil ($mg \cdot kg^{-1}$)		0.075	0.15
Age (yr)		46.8±14.0	45.5±12.5
Height (cm)		157.7±10.2	153.4±5.7
Body weight (kg)		56.0±5.5	54.9±7.5
pHa	before	7.40±0.02	7.41±0.02
	after	7.40±0.02	7.41±0.02
$Paco_2$	before	37±3	35±4
(mmHg)	after	37±2	35±3
Pao_2	before	89±7	93±6
(mmHg)	after	89±5	94±3
BE	before	−1.4±1.5	−1.1±1.6
($mEq \cdot L^{-1}$)	after	−1.2±1.4	−1.3±1.7

All values are mean±SD.

Data were expressed as mean±SD. Results were analyzed statistically using Student's t test for paired data to compare the values before and after verapamil in each group, and for unpaired data to compare the values between both groups. P value less than 0.05 was considered as statistically significant.

Results

Age, height, weight, and values of arterial blood analyses were comparable in the two groups (table 1). There were also no significant differences between the two groups in the mean control values of CSFP, MAP, CPP (table 2), and HR (86.6±15.1 and 84.5±20.3 $beats \cdot min^{-1}$ in group 1 and 2, respectively).

Verapamil, in doses of $0.075\ mg \cdot kg^{-1}$ and $0.15\ mg \cdot kg^{-1}$ increased CSFP in every patient (fig. 1). An increase in CSFP occurred almost simultaneously with decreases in MAP, which attained the maximal changes in approximately 0.5 to 1.5 min after the injection of verapamil, then gradually returned to the control values in 15 min (fig. 1). CSFP after verapamil

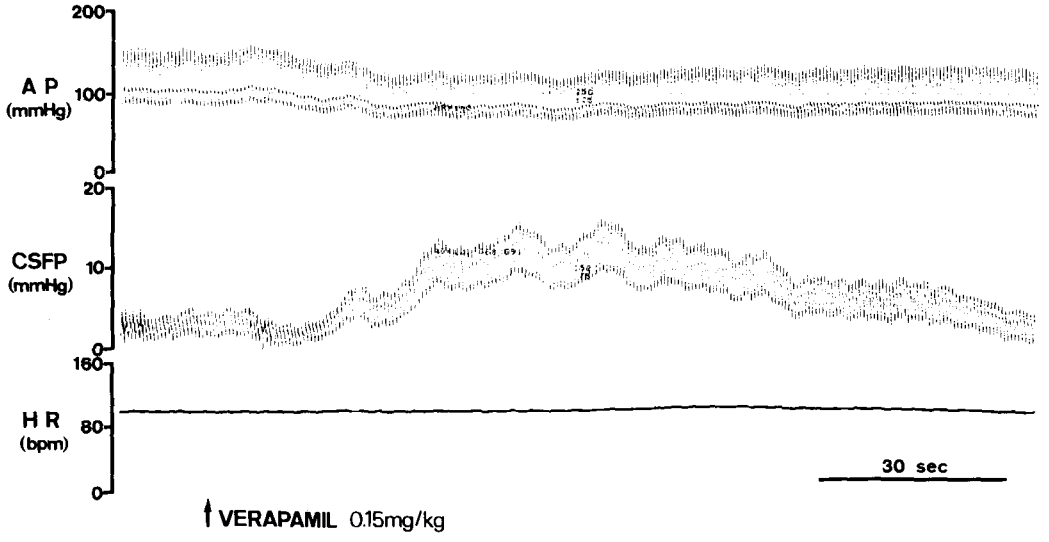

Fig. 1. Tracings showing changes in arterial blood pressure (AP), cerebrospinal fluid pressure (CSFP), and heart rate (HR) after verapamil 0.15 mg·kg^{-1}, as a bolus.

Table 2. Control values of cerebrospinal fluid pressure (CSFP), mean arterial blood pressure (MAP) and cerebral perfusion pressure (CPP) and values during maximal changes following verapamil

		Group 1 (Verapamil, 0.075 mg·kg^{-1})	Group 2 (Verapamil, 0.15 mg·kg^{-1})
CSFP	Control	6.0±3.5	6.2±3.1
(mmHg)	Maximal Changes	10.5±4.3*	12.6±3.8*
MAP	Control	103.0±8.8	102.5±12.7
(mmHg)	Maximal Changes	85.5±8.6*	75.0±9.7*+
CPP	Control	96.9±7.9	96.2±11.4
(mmHg)	Maximal Changes	76.0±8.2*	62.4±8.2*‡

All values are mean±SD.
*$P<0.01$ compared to control values.
+$P<0.05$ compared to Group 1.
‡ $P<0.01$ compared to Group 1.

increased to the levels significantly above control ($P<0.01$, table 2), whereas MAP and CPP significantly decreased below the control values ($P<0.01$), and the changes of the latter two were dose-related (table 2). Maximal changes in CSFP following verapamil, 0.075 mg·kg^{-1} and 0.15 mg·kg^{-1}, were 195±65% and 226±85%, respectively. The increase of CSFP from the baseline after verapamil appeared to be greater in group 2 than in group 1 (6.3±2.3 mmHg vs. 4.4±2.0 mmHg). However, there was no statistically significant difference between the two groups. The HR showed variable changes; initial increases followed by decreases from the controls in eleven out of twenty patients, increases followed by gradual return to the baselines in eight patients, and a sustained decrease from the control was seen in one patient. No significant change from control values was observed in arterial blood gas tensions after

verapamil in the both groups (table 1). During the study, there were no adverse reactions such as bradycardia, conduction disturbances, headache, facial flushing, and severe hypotension to verapamil in any of the patients.

Discussion

The present study showed that an intravenous bolus injection of verapamil 0.075–0.15 $mg \cdot kg^{-1}$, increased the CSFP consistently in non-anesthetized patients with no intracranial lesions. However, the increase was not significant clinically, and we observed no case of CPP less than 40 mmHg, a critical level for development of cerebral ischemia. Thus, the effects of verapamil upon CSFP and cerebral circulation appears to be clinically insignificant in normal patients.

Verapamil is a synthetic papaverine derivative[16], and its preferable site of action has been suggested to be the cerebral vessels. It has been reported that verapamil in vitro caused a dose-related relaxation of the arteries contracted with $PGF_{2\alpha}$ which were greater in cerebral than in other arteries[1]. Subsequently, Rosenblum[17] confirmed in their in vivo experiments using mice that the constriction of pial arterioles with $PGF_{2\alpha}$ was inhibited by local application or i.p. injection of verapamil. Accordingly, the increases in CSFP following verapamil observed in the present study seems to be ascribed to cerebral vasodilation resulting in an increase of cerebral blood volume. Since Bedford and co-workers[14] reported that verapamil produced increases of ICP in patients with supratentorial brain tumors, other investigators also have examined the effects of calcium entry blockers, such as nifedipine or diltiazem upon ICP in anesthetized cats and have obtained similar results[12,13]. For normal humans, the authors have suggested that the influence of nicardipine, one of the calcium entry blockers, upon CSFP is of little clinical significance[15]. This idea also seems to be applicable to the effects of verapamil on CSFP.

Variability in changes of HR after verapamil, usually giving rise to initial increases followed by decreases observed in the present study can be explained on the basis of the following concept. In general, the HR responses to vasodilators are determined by an interaction of reflexly increased sympathetic activities via baroreceptors and the direct actions upon the special excitatory conductive system of the heart[16]. Verapamil has more inhibitory actions upon the sinoatrial and atrioventricular nodes as compared with such other calcium entry blockers as nifedipine and nicardipine[18–20]. Therefore, the initial acceleration in HR might be caused by relatively increased sympathetic outflows, thereafter, the negative chronotropic effect of verapamil per se might in turn counteract these sympathetic reflexes to the hypotensive effect.

Dose-related decreases in MAP and CPP after intravenous verapamil (table 2) may suggest that calcium entry blockers including verapamil should be carefully administered or avoided in patients with intracranial hypertension, especially in such circumstances as in systemic hypotensive or hypovolemic states. This suggestion is based on the assumption that severe hypotension with increased ICP may more pronouncedly compromise the cerebral circulation, possibly resulting in cerebral ischemia.

It is concluded that verapamil in doses of 0.075–0.15 $mg \cdot kg^{-1}$ has no neurological side effects regarding its effect upon CSFP, and does not cause any harmful sequelae in the absence of intracranial hypertension. However, it must be stressed that verapamil may increase CSFP to undesirable levels and should be avoided in patients with decreased intracranial compliance.

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