Adverse impact of a calcium entry-blocker (verapamil) on intracranial pressure in patients with brain tumors

ROBERT F. BEDFORD, M.D., RALPH DACEY, M.D., H. RICHARD WINN, M.D., AND CARL LYNCH III, M.D., PH.D.

Departments of Anesthesiology and Neurological Surgery, University of Virginia School of Medicine, Charlottesville, Virginia

In order to examine the effects of verapamil on intracranial pressure (ICP) in patients with compromised intracranial compliance, five hypertensive patients with supratentorial tumors were given verapamil, 5 mg intravenously, at the time of anesthesia induction. Within 4 minutes, ICP increased 67% from 18 + 4 mm Hg (standard error) to 27 + 5 mm Hg (p < 0.05), whereas mean arterial pressure decreased 20% from 111 + 7 mm Hg to 89 + 4 mm Hg (p < 0.05), and cerebral perfusion pressure (CPP) decreased 33% from 93 + 11 mm Hg to 62 + 6 mm Hg (p < 0.05). The increases in ICP responded promptly to hyperventilation and intravenous lidocaine (1.5 mg/kg). A control group of five hypertensive patients with supratentorial tumors received the same anesthetic agents without verapamil. In this group, ICP and CPP were unchanged. The authors conclude that calcium entry-blockers, such as verapamil, should be avoided in patients with compromised intracranial compliance unless ICP is being monitored and proper therapy for intracranial hypertension can be rapidly instituted.

KEY WORDS • brain tumor • intracranial pressure • verapamil • calcium blocker

Calcium entry-blocking agents (CEB's) have achieved widespread clinical use for the treatment of supraventricular tachyarrhythmias, chronic stable angina, myocardial ischemia associated with coronary vasospasm, and arterial hypertension. In addition, recent investigations indicate that CEB's may be promising agents for the treatment of cerebral vasospastic and ischemic disorders because of their potent vasodilating effect on the cerebral circulation. Although the effects of CEB's on intracranial pressure (ICP) have not been reported previously, we thought that hypertensive patients with brain tumors who receive CEB's should have their ICP monitored, since many vasodilating drugs are known to cause intracranial hypertension in this setting. This report summarizes our findings.

Clinical Material and Methods

Ten hypertensive patients with supratentorial mass lesions greater than 4 cm in diameter, as revealed by computerized tomography, were the subjects of this investigation. The protocol was reviewed by our institution's human studies committee, and detailed informed consent was obtained from both the patients and their nearest relative on the evening before surgery. Upon arrival in the operating room, a 1% lidocaine solution was injected into the scalp and a subarachnoid bolt was placed for monitoring ICP on the side contralateral to the brain tumor. A No. 20 radial artery catheter was also placed, and intracranial and arterial pressures were transduced and recorded continuously.*

After control measurements of cardiovascular variables and ICP were obtained, general anesthesia was induced with thiopental (3 mg/kg intravenously), nitrous oxide (70% in O2), and pancuronium (0.1 mg/kg intravenously). Ventilation was controlled by face mask to maintain a constant end-tidal CO2 fraction. In five

* Bentley Model 800 transducer and Brush Model 440 recorder manufactured by Gould Instruments, Inc., 3631 Perkins Avenue, Cleveland, Ohio.
Effect of verapamil on ICP in brain-tumor patients

patients chosen randomly by lot, verapamil (5 mg) was given as an intravenous bolus to decrease arterial pressure and heart rate. The remaining five patients received the same anesthetic agents and a saline placebo. Endotracheal intubation and other procedures known to increase ICP and arterial pressure were deferred until after the peak effects of verapamil were observed. Four minutes after induction of anesthesia, increases in ICP were aborted by increasing alveolar ventilation and administering lidocaine (1.5 mg/kg intravenously) as illustrated in Fig. 1. Peak changes in ICP and cardiovascular variables were compared with baseline values using Student's t-test for paired data. Intergroup comparisons were made using Student's t-test for unpaired data (p < 0.05 was regarded as significant).

Results

The two groups of patients were similar with regard to intracranial pressure-volume relationship: with a 1-ml volume challenge, ICP increased 5.0 ± 1.8 mm Hg (standard error) in the verapamil group and 5.4 ± 1.5 mm Hg in the control group. Patients who received verapamil sustained significant increases in ICP and decreases in mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) (MAP - ICP), whereas in the control group ICP decreased and mean CPP was statistically unchanged (Table 1). Although MAP decreased in the control group, CPP was significantly higher in these patients than in the group that received verapamil. It was not possible to determine a duration of action for the peak effect of verapamil on ICP because all instances of increased ICP were treated promptly at 4 minutes after induction of anesthesia with hyperventilation and intravenous administration of lidocaine.

We found no evidence that verapamil treatment was any more effective than standard induction of thiobarbiturate anesthesia in treating arterial hypertension. Both groups of patients sustained reductions in rate-pressure product (heart rate x systolic pressure) below values known to cause myocardial ischemia in patients with coronary artery disease. No patient developed evidence of neurological deficit in the postoperative period which could be related to the observed increases in ICP.

Discussion

Contrary to the enthusiastic reports extolling the potential benefits of calcium entry-blocking agents (CEB's) on cerebral circulation in ischemia and trauma, our findings suggest that use of verapamil may be contraindicated in patients with space-occupying intracranial lesions or, perhaps, other causes of compromised intracranial compliance. In vitro studies of canine vessels contracted with prostaglandin F2α or potassium have shown that verapamil tends to cause preferential dose-dependent relaxation of cerebral vessels over coronary and mesenteric vessels, whereas sodium nitroprusside and nitroglycerin caused equal relaxation of arteries from different vascular beds. Since both nitroprusside and nitroglycerin cause marked increases in ICP when intracranial compliance is impaired, it is not surprising that the ICP response to verapamil seen clinically is rapid and profound. Fortunately, we found that these increases in ICP are readily attenuated by hyperventilation and intravenously administered lidocaine, even though Harris, et al., noted impaired cerebrovascular response to arterial pCO2 changes in baboons treated with the CEB, nimodipine. In the present circumstance, where ICP was elevated and arterial pressure was low, intravenous lidocaine was a logical alternative modality for rapidly controlling ICP without further depressing arterial pressure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Levels</th>
<th>4 Mins After Anesthesia</th>
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<tbody>
<tr>
<td></td>
<td>Verapamil Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>18 ± 4</td>
<td>18 ± 3</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>111 ± 7</td>
<td>113 ± 3</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>93 ± 11</td>
<td>95 ± 5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>91 ± 12</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>RPP (mm Hg-beats/min)</td>
<td>15,107 ± 2267</td>
<td>12,656 ± 1209</td>
</tr>
</tbody>
</table>

* All values are means ± standard error. Significance: † = p < 0.05 versus control group; ‡ = p < 0.05 versus baseline values. ICP = intracranial pressure; HR = heart rate; RPP = rate-pressure product; MAP = mean arterial pressure; CPP = cerebral perfusion pressure.
Intracranial pressure is thought to increase in this setting, primarily because reduced cerebrovascular resistance causes an increase in cerebral blood volume at a time when intracranial compliance is impaired. We believe it unlikely that the increases observed in ICP would have occurred without administration of verapamil. Induction of thiopental-nitrous oxide anesthesia with controlled ventilation has been shown repeatedly to produce decreases in ICP in patients with brain tumors as long as noxious stimuli such as endotracheal intubation are avoided.\(^3\)

The clinical implication of these observations seems clear. Calcium entry-blocking agents should not be given for hemodynamic or cerebrovascular indications to patients with a compromised intracranial pressure-volume relationship unless ICP is being monitored and appropriate therapeutic measures can be instituted rapidly to prevent intracranial hypertension and/or systemic hypotension, which might result in compromise of CPP.

References


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Address reprint requests to: Robert F. Bedford, M.D., Box 238, University of Virginia Medical Center, Charlottesville, Virginia 22908.