Effect of intracisternal phentolamine on cerebral blood flow after subarachnoid injection of blood

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The hydrogen clearance method was used to measure total and focal cerebral blood flow (CBF) in the monkey before and for 5 hours after a simulated subarachnoid hemorrhage (SAH). Some monkeys also received 0.2 to 1.0 mg/kg phentolamine intracisternally 3 hours after SAH. Results show that SAH did not change cerebrovascular resistance, but as cerebral perfusion pressure decreased, CBF fell transiently. Phentolamine injected intracisternally 3 hours after SAH produced a significant fall in arterial blood pressure; cerebrovascular resistance did not change but CBF decreased significantly. These data indicate that intracisternal phentolamine cannot be considered potentially useful to treat ischemic encephalopathy after SAH.

KEY WORDS • vasospasm • spasmolysis • phentolamine • alpha-adrenergic blockade • hydrogen clearance • cerebral blood flow • subarachnoid hemorrhage

SPASM of the arteries of the brain has been implicated as the principal cause of ischemic encephalopathy that often delays or prevents recovery from a spontaneous subarachnoid hemorrhage (SAH). 1,4,6,7,10,21 Ischemic encephalopathy has been treated with diverse spasmolytic drugs administered parenterally, but the results have been equivocal at best. 2,4,10,19,24 It has been observed that spasmolytic drugs seem to be more effective as vasodilators when they are applied topically to vessels in spasm or added directly to the cerebrospinal fluid (CSF) than when they are blood-borne. 4,5,7,13,14 With these observations in mind, Martins and Wiley 17,18 proposed using spasmolytics intracisternally. They subsequently found that phentolamine, an alpha-adrenergic blocking agent and potent vasodilator, is nontoxic to the intact rhesus monkey when it is given intracisternally in relatively large doses. 18 Martins and Wiley concluded that phentolamine given intracisternally warranted further experimental evaluation as possible therapy for ischemic encephalopathy complicating SAH.

We report the results of an investigation to
A. N. Martins, et al. determine the effect of intracisternal phen tolamine on cerebral blood flow in the rhesus monkey after a simulated SAH.

Materials and Methods

Rhesus monkeys, unselected as to sex and weighing between 3 and 5 kg, were anesthetized initially with 50 mg ketamine and 0.5 mg atropine sulfate given intramuscularly, and 50 mg pentobarbital given intravenously. After the monkeys were intubated with auffed endotracheal tube, catheters were placed into the femoral artery and vein from which we monitored mean arterial blood pressure (MABP) continuously, administered drugs, and sampled arterial blood for immediate direct gas and pH analysis before and after each cerebral blood flow (CBF) determination. Subsequently, the monkey was positioned sphinx-like in a stereotaxic apparatus. A 19-gauge needle attached to a polyethylene tube was passed into the cisterna magna, through which we measured intracranial pressure (ICP) continuously and obtained 1 ml of cerebrospinal fluid (CSF) for later use.

Respirations were controlled at 40 to 44/min with a small-animal respirator; tidal volume was 45 cc, and the inspiratory phase of the respiratory cycle was 35% of the total. Anesthesia was maintained with an inspired gas mixture of 70% nitrous oxide and 30% oxygen. Enough CO₂ was added to keep arterial pCO₂ as close as possible to 32 mm Hg, which is normal for the awake, acclimatized rhesus monkey.22 Arterial pO₂ ranged between 135 and 150 mm Hg. After an initial intravenous loading dose of 2 mg of tubocurarine chloride, lactated Ringer's solution, to which was added 0.06 mg/ml of tubocurarine chloride, was infused intravenously by pump at 16 ml/hr to maintain both fluid balance and muscular paralysis for the entire experiment. A heated pad kept the body temperature (rectal) between 37° and 39° C.

Cerebral Blood Flow Measurement

Both local and total CBF were measured by the hydrogen clearance technique as we have previously detailed.11,12,16,25 Local CBF was measured with five polarographical electrodes of fine platinum wire supported by glass capillary tubes placed stereotaxically into the occipital and parietal lobes, and into the thalamic, reticular, and hypothalamic areas of the diencephalon. Tissue electrodes were implanted 1 to 7 days before the experiment and affixed to the skull with dental acrylic. Although coordinates of the target areas were not changed throughout the investigation, technical difficulties resulted in some electrodes being off target by as much as 2 mm, which accounts in part for some of the variability of CBF recorded by a particular electrode from animal to animal. Figure 1 shows the areas of the brain from which we recorded local tissue CBF.

Total CBF was measured by following the clearance of hydrogen from blood flowing through the torcular Herophili with a polarographical electrode passed transdurally into the torcular at the start of the experiment. Cerebral blood flow determinations were begun by adding hydrogen (5 to 10 vol %) to the inspired gas mixture for 10 minutes, after which it was stopped abruptly. The first 40 seconds of the clearance curves were discarded and the remainder analyzed to give CBF values.11,12,16,25

Experimental Procedure

More than 2 hours elapsed between the injection of ketamine and pentobarbital and the first CBF determination. During this period vital signs and blood gases stabilized and all operative procedures were completed. Thereafter, CBF determinations were made hourly for the ensuing 7 hours.

Animals were allocated to three groups:

Group I = Controls with no SAH (5 monkeys),
Group II = SAH at end of second hour (6 monkeys),
Group III = SAH at end of second hour and phentolamine 3 hours later (8 monkeys).

To simulate an SAH in monkeys of Groups II and III, we drilled a hole 1 mm in diameter through the frontal bone in the midline, 40 mm anterior to the interaural line. From this point of entry, a 22-gauge spinal needle was advanced with the aid of a stereotaxic guide along the mid-sagittal plane at an angle of 45° to Reid's (infraorbital-meatal) line to a depth of 26 mm from the dura. This usually positioned the point of the needle in the prechiasmatic subarachnoid space. After two serial baseline CBF determinations were completed, 4 ml of blood was withdrawn from

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FIG. 1. Location of tissue electrodes from which local blood flow was determined: A = occipital lobe; B = parietal lobe; C = diencephalic reticular formation on the left and thalamus on the right; and D = hypothalamus.

the femoral artery and immediately injected by hand into the prechiasmatic cistern over about a 5-minute period. The speed of the injection was adjusted so as to keep the ICP at least 30 mm Hg below MABP. We then made CBF determinations during the 5 hours following the simulated SAH.

Three hours after the SAH, monkeys of Group III received intracisternally 0.2 mg to 1.0 mg/kg phentolamine mesylate* injected within a few seconds through the needle previously placed into the cisterna magna. The solution of phentolamine was freshly prepared immediately before use by dissolving 5 mg of phentolamine in 0.5 ml of autologous CSF obtained at the start of the experiment. The dose of phentolamine was varied by varying the volume of solution injected. Two CBF determinations were made during the 2 hours after the phentolamine injection, the first one beginning about 10 minutes after the injection and the second an hour later.

At the conclusion of each experiment, the animal was killed with an overdose of pentobarbital, its brain removed and examined to determine the location of the injected blood. Data from animals receiving anything but an essentially pure SAH were discarded.

Results

Blood gases and pH remained stable throughout the experiments in all animals of each group. In Groups II and III SAH was generally extensive and confluent throughout the basal cisterns and Sylvian fissure, and in some animals, blood had gone into the interhemispheric fissure and over the convexities.

Group I Monkeys

In the five control monkeys, MABP and ICP remained stable; MABP ranged between 98 and 115 mm Hg, while the mean ICP

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In the eight monkeys with SAH at end of the second hour and phentolamine 3 hours later, MABP remained stable and not significantly different from that in Groups I and II until after the phentolamine injection when the blood pressure began to fall within 5 minutes, reached its nadir within 30 minutes, and rose slowly during the next hour. The fall from 115 mm Hg to 84 mm Hg was statistically significant (p < 0.01). Mean ICP remained unchanged by phentolamine. Total CBF and local CBF in all areas fell after phentolamine, sometimes significantly (p = 0.05 or less); but CVR was not changed significantly by phentolamine (Figs. 2 and 3, and Table 1).

Groups II Monkeys

In the six monkeys with SAH at end of the second hour, MABP remained stable and not significantly different from the controls. Mean ICP increased from 9 mm Hg to 35 mm Hg after SAH and remained high (statistically significant: p < 0.05). After SAH, total and local CBF fell, recovered, and then fell again (Fig. 2). Cerebrovascular resistance (CVR) did not change significantly as a result of the SAH and paralleled that of the control group (Fig. 3).

Discussion

Contrary to expectations, phentolamine given intracisternally after SAH reduced rather than increased CBF, and CVR remained unchanged. Consequently, we have concluded that intracisternal phentolamine may no longer be considered as potentially useful to treat ischemic encephalopathy complicating SAH.

As previously noted, arterial blood pressure begins to fall within 5 minutes of an intracisternal injection of phentolamine. The mechanism for this hypotensive effect is not clear. It may simply be due to peripheral alpha-adrenergic blockade. In this case, we must assume that phentolamine diffuses from the CSF into the bloodstream by way of the

Fig. 2. Graph summarizing mean CBF changes in all three groups. Arrows indicate SAH at 2 hours and intracisternal phentolamine at 5 hours. Stars indicate a statistically significant difference (p < 0.05) from 5-hour value.

Fig. 3. Mean cerebrovascular resistance in all three groups. Group I = controls, Group II = SAH at 2 hours, Group III = SAH at 2 hours and phentolamine intracisternally 3 hours later.
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**TABLE 1**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Hour 1</th>
<th>Hour 2</th>
<th>Hour 3</th>
<th>Hour 4</th>
<th>Hour 5</th>
<th>Hour 6</th>
<th>Hour 7</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After SAH</td>
<td>After SAH</td>
<td>After SAH</td>
<td>After Phentolamine</td>
<td></td>
<td></td>
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<tr>
<td>cerebral blood flow†</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>total (N = 8)</td>
<td>66 ± 7.8</td>
<td>67 ± 7.3</td>
<td>59 ± 8.1</td>
<td>73 ± 11</td>
<td>75 ± 12</td>
<td>54 ± 10‡</td>
<td>54 ± 12‡</td>
</tr>
<tr>
<td>occipital (N = 7)</td>
<td>48 ± 13.4</td>
<td>51 ± 14.8</td>
<td>44 ± 8.1</td>
<td>52 ± 9.0</td>
<td>52 ± 8.9</td>
<td>39 ± 11.2‡</td>
<td>35 ± 11.4‡</td>
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<tr>
<td>parietal (N = 6)</td>
<td>51 ± 7.9</td>
<td>57 ± 10.8</td>
<td>36 ± 7.0</td>
<td>46 ± 10.0</td>
<td>41 ± 8.3</td>
<td>20 ± 6.5‡</td>
<td>18 ± 4.8‡</td>
</tr>
<tr>
<td>reticular (N = 6)</td>
<td>62 ± 9.8</td>
<td>71 ± 12.9</td>
<td>59 ± 14.1</td>
<td>73 ± 20.1</td>
<td>69 ± 16.0</td>
<td>36 ± 7.3</td>
<td>37 ± 9.3</td>
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<td>thalamic (N = 8)</td>
<td>94 ± 3.6</td>
<td>98 ± 14.2</td>
<td>78 ± 19.1</td>
<td>98 ± 25.8</td>
<td>93 ± 18.0</td>
<td>62 ± 9.6</td>
<td>47 ± 11.4</td>
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<tr>
<td>hypothalamic (N = 6)</td>
<td></td>
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<tr>
<td>MABP (mm Hg) (N = 8)</td>
<td>109 ± 8</td>
<td>115 ± 12</td>
<td>111 ± 9</td>
<td>110 ± 8</td>
<td>115 ± 7</td>
<td>84 ± 8‡</td>
<td>97 ± 8‡</td>
</tr>
<tr>
<td>ICP (mm Hg) (N = 8)</td>
<td>7 ± 2</td>
<td>10 ± 3</td>
<td>26 ± 7</td>
<td>22 ± 5</td>
<td>20 ± 5</td>
<td>20 ± 6</td>
<td>22 ± 8</td>
</tr>
<tr>
<td>CVR (mm Hg/ml/100 g/min) (N = 8)</td>
<td>1.6 ± .3</td>
<td>1.6 ± .3</td>
<td>1.6 ± .1</td>
<td>1.4 ± .1</td>
<td>1.4 ± .1</td>
<td>1.5 ± .3</td>
<td>1.4 ± .2</td>
</tr>
</tbody>
</table>

* All numbers = mean ± SEM; N = number of experiments; MABP = mean arterial blood pressure; ICP = intracranial pressure; CVR = cerebral vascular resistance.
† Unit of measurement = ml/100 gm/min.
‡ Statistically significant from 5 hr value (p = .05 or less; paired t test).

Cognizant of the report of Petruk, et al., we proceeded with this investigation under the assumption that CBF falls immediately after a subarachnoid injection of blood. On the contrary, we found that if ICP and MABP remain stable, blood injected into the intracranial subarachnoid space neither consistently increased CVR nor reduced CBF during the 5-hour observation period, which accounts for the high mean CBF values noted after SAH in monkeys given phentolamine. These observations suggest that the spasmodenic activity of fresh whole blood, and the vasoconstriction it may cause shortly after entering the CSF, probably play a limited role in the pathogenesis of ischemic encephalopathy that develops acutely after an SAH.

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References


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