Control of Cerebral Vasospasm by Parenteral Phenoxybenzamine

BY EUGENE S. FLAMM, M.D., M. GAZI YASARGIL, M.D., AND JOSEPH RANSOHOFF, M.D.

Abstract:
Cerebral vasospasm has been studied in the basilar artery of the cat. The ability of alpha adrenergic blocking agents to prevent and alleviate spasm produced by the application of blood to the basilar artery has been investigated.

Parenteral phenoxybenzamine is effective in preventing spasm under these experimental conditions when given in doses of 12 mg/kg provided at least two hours elapse between the administration of the drug and the application of the blood. The drug has been found effective up to 24 hours after parenteral administration.

The systemic response to alpha adrenergic blockade and the effects on spasm of the basilar artery produced by different doses at intervals from 1 to 44 hours after the administration of the drug are presented.

Although parenteral phenoxybenzamine is effective in preventing spasm from subarachnoid blood, it does not prevent spasm from mechanical manipulation of the vessels. This would indicate that mechanisms other than adrenergic stimulation itself may be operative in cerebral vasospasm. The alteration of spasm from blood and mechanical manipulation by other alpha adrenergic blocking agents has been studied and the possible modes of action of these drugs are discussed.

Additional Key Words
subarachnoid hemorrhage alpha adrenergic blockade phenolamine

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Although the presence of nerve fibers within the walls of cerebral vessels has been known for 40 years since the work of Forbes, Wolff, Penfield, and others, renewed interest in the role of adrenergic fibers has developed in the past few years.1-4 Electron microscopy and special staining techniques have been used to demonstrate an extensive plexus of adrenergic fibers and the presence of catecholamines within the walls of the major cerebral vessels of many animals.5-9 This information has been applied to the study of cerebral vasospasm following subarachnoid hemorrhage in the laboratory as well as in clinical situations. Several reports of the use of alpha adrenergic blocking agents in the treatment of patients with cerebral vasospasm have appeared.10,11 Fraser et al. have studied the use of these agents to modify experimental cerebral vasospasm by topical applications of the drugs.12 The present study deals with the effects of a systemic alpha adrenergic blocking agent on experimental cerebral vasospasm.

Methods
Adult cats ranging in weight from 1.4 to 3.5 kg were used. The animals were anesthetized with intramuscular ketamine and pentobarbital and maintained on a volume respirator through a
A transclidean approach to the basilar artery, using an operating microscope, was used.13,15 After hemostasis had been obtained, the dura and then the arachnoid around the basilar artery were opened. The arachnoid on both sides of the basilar artery was incised but not stripped from the vessel. This usually produced some degree of spasm which was allowed to clear spontaneously in 10 to 15 minutes. During this period, the vessels were covered with isotonic saline at body temperature.

After all mechanically induced spasm had disappeared, the field was suctioned dry. Photographs were taken through the operating microscope at a magnification of 25X. A scale in 0.5-mm divisions was included in the field to assist in evaluating changes in vessel size. Photographs were again taken after 3 ml of fresh arterial blood had been applied to the basilar artery for three minutes. Changes in vessel size were measured from the photographs taken before and after the application of blood. This was done by projecting the slides and making tracings of the enlarged

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**TABLE 1**

| Changes in Diameter of Basilar Artery Following the Application of Blood |

<table>
<thead>
<tr>
<th>Controls</th>
<th>No.</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylbenzamine (parenteral)</td>
<td>11</td>
<td>-55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Time (hour after infusion)</th>
<th>% change</th>
<th>Presence of alpha blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>2</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>5</td>
<td>-3.5</td>
</tr>
<tr>
<td>12</td>
<td>22</td>
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<td>3</td>
<td>-45</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>5</td>
<td>-42</td>
</tr>
<tr>
<td>1-5</td>
<td>2-6</td>
<td>5</td>
<td>-55</td>
</tr>
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</table>

tracheostomy. Femoral arterial and venous catheters were inserted and used for the measurement of blood pressure and administration of drugs. Temperature of the animals was maintained at 37°C and monitored with a rectal probe. EKG was recorded also.

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**FIGURE 1**

CONTROL OF CEREBRAL VASOSPASM

images. Results are reported as percentage change in the diameter of the blood column.

Parenteral (I.V.) phenoxybenzamine was administered to 34 cats in doses ranging from 1 to 12 mg/kg. The drug was given in 100 ml of normal saline over a period of 30 to 60 minutes. The animals received the drug from 30 minutes to 44 hours before the application of blood to the basilar artery.

Results

The results are summarized in table 1. In 11 animals who received no phenoxybenzamine, there was a mean decrease in the diameter of the blood column of the basilar artery of 55% with a range of 44 to 67% (fig. 1). In 11 cats, blood was applied to the basilar artery two hours after the completion of an infusion of phenoxybenzamine containing 12 mg/kg of the drug. No spasm was seen in these animals. If blood was applied sooner than one and one-half to two hours after completion of the infusion, spasm was readily produced.

The same dose of phenoxybenzamine was given to five animals six hours before the application of blood; another group of five animals received the drug 20 to 22 hours before blood was applied. Essentially, no spasm was seen in these animals (fig. 2). A mean decrease of 3.5% in the six-hour group and 4.3% in the 22-hour group was measured from the photographs. During the operative procedure, no spasm was appreciated visually.

Three cats received 12 mg/kg of phenoxybenzamine 42 hours before the artery was exposed to blood. In these cats, a decrease of 45% in diameter of the basilar blood column was measured.

No prevention of spasm was observed when lower doses of phenoxybenzamine were given. Five animals received 6 mg/kg and five animals received 1 to 5 mg/kg. Spasm with reduction of the blood column by 42% and 55%, respectively, was found when blood was
applied two to six hours after completion of the infusion (fig. 3).

The systemic effects of phenoxybenzamine were reflected in the lowering of both the systolic and diastolic pressures with a widening of the pulse pressure. The heart rate remained unchanged (table 2). This change in blood pressure was seen 15 minutes after the start of the infusion. Once the blood pressure changed, it remained quite stable at the new level for six to eight hours. In those animals receiving 12 mg/kg, administration of norepinephrine produced a marked tachycardia but no change in the blood pressure, thus indicating the adequacy of the alpha adrenergic blockade. After 24 hours the blockade was still present, although the mean blood pressure had returned toward the pretreatment values. In those animals studied 42 to 44 hours after completion of the infusion, the blood pressure had

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tr>
<td><strong>Systemic Effects of Parenteral Phenoxybenzamine</strong></td>
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<tr>
<td>----------</td>
</tr>
<tr>
<td><strong>Before drug</strong></td>
</tr>
<tr>
<td>Mean systolic BP</td>
</tr>
<tr>
<td>Mean diastolic BP</td>
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<tr>
<td>Mean heart rate</td>
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</table>

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returned to normal levels, and no evidence of an alpha adrenergic blockade was seen when norepinephrine was given.

Discussion

In a previous report, we noted that while phenoxybenzamine prevented spasm from the application of blood, it was not effective in preventing spasm induced by mechanical manipulation of the basilar artery. We found that another alpha adrenergic blocking agent, phentolamine, was effective in alleviating and preventing mechanically induced spasm when the drug was applied topically to the basilar artery. The different response to these two alpha adrenergic blocking agents also has been noted in the 22-hour group of animals. Even though alpha adrenergic blockade is present after the parenteral administration of phenoxybenzamine, no protection is offered against spasm from manipulation of the vessels although the application of blood fails to produce spasm. The effectiveness of phentolamine against mechanical spasm indicates that this drug may prevent spasm by mechanisms other than alpha adrenergic blockade. In vitro studies in monkeys and dogs have shown that the basilar artery is not responsive to either alpha or beta adrenergic stimulation when these agents are added to an isolated segment of the vessel.

The interval of about one to two hours before blockade becomes established has been interpreted as the time necessary for the drug to become fixed at receptor sites in the vessel wall. Several observations indicate that other mechanisms may be involved. The changes in blood pressure were observed 15 minutes after the start of the infusion. This was not dependent on the rate of administration of the drug and may indicate that phenoxybenzamine also acts directly on resistance vessels as has been postulated for phentolamine.

Cummins and Griffith have reported encouraging results with phenoxybenzamine administered through the carotid artery in patients with cerebral vasospasm. They gave a total of 20 mg into the carotid artery. This route of administration for a dose considerably lower than that required to establish adrenergic blockade may not allow sufficient time for the drug to become fixed at receptor sites of the cerebral vessels. This too may indicate that the drug acts directly on the smooth muscle of the vessel walls.

Thus, the evidence for a role of alpha adrenergic stimulation in the production of cerebral vasospasm has not been completely established. At present, we can only conclude that while phenoxybenzamine is effective in preventing experimental cerebral vasospasm for up to 24 hours when administered in doses of 12 mg/kg, the exact mechanism of action is not clear. Further studies are necessary to determine if it operates solely by alpha adrenergic blockade or on the vascular smooth muscle, or both.

The clinical use of phenoxybenzamine and other alpha adrenergic blocking agents seems warranted, based on the preliminary clinical and laboratory studies. The consequences of systemic alpha adrenergic blockade in patients with cerebral vasospasm must be carefully studied before the efficacy of these drugs in treating patients with spasm after subarachnoid hemorrhage can be established.

References


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