Papaverine Hydrochloride and Experimental Hemorrhagic Cerebral Arterial Spasm

BY AKIO KUWAYAMA, M.D.1 NICHOLAS T. ZERVAS, M.D.2 AKIRA SHINTANI, M.D.3 AND KENNETH S. PICKREN, B.S.C.4

Abstract:
Papaverine hydrochloride and experimental hemorrhagic cerebral arterial spasm

Chronic hemorrhagic spasm of the basilar artery was produced in beagle dogs by introducing blood into the cisterna magna. Spasm was evaluated by means of vertebral angiography. Papaverine hydrochloride was administered intravenously, intracisternally as well as intra-arterially. The intracisternal route was the more effective in combating spasm but the effect was transitory. The results suggest that the treatment of spasm by chemical means in subarachnoid hemorrhage using agents currently available would require continuous topical application.

ADDITIONAL KEY WORDS: aneurysm basilar artery angiography subarachnoid hemorrhage

The injection of autogenous arterial blood into the cisterna magna of the dog will induce arterial spasm at the base of the brain, especially of the basilar artery. Constriction develops rapidly, subsides somewhat in a few hours but recurs within a few days and is stable for a week or so.

Several recent studies1-8 have been concerned with the effect of drugs on acute hemorrhagic vasospasm. The study reported below was directed at achieving a means of reducing chronic arterial spasm in the dog. In particular the effect of papaverine hydrochloride (PPV) by different routes of administration was studied.

Methods
Forty-nine beagle dogs weighing 7 to 15 kg were used in the various phases of this study. They were anesthetized with intravenous pentobarbital following premedication with intramuscular Ketaset.6 Spontaneous respiration was permitted.

Body temperature was kept constant with an electric blanket, and arterial blood pressure was continuously monitored. Following cannulation of one vertebral artery, the dogs were placed in a stereotaxic frame in the prone position. A control angiogram was taken using 2 ml of Renografin-76.7 Two milliliters of arterial blood was injected into the cisterna magna. The dogs were tilted with the tail up for ten minutes to facilitate the blood clot sinking to the base of the brain. In some dogs a repeat angiogram was obtained immediately, but otherwise the cannula was removed and the site of cannulation was sutured.

Two to four days later a repeat angiogram was performed through the same vertebral artery. After confirming the presence of chronic vasospasm of the basilar artery, PPV (15 mg) was injected by three different routes, intravenously, intra-arterially or intracisternally. The drug was diluted to 2 ml with normal saline and warmed to 37°C. Intravenous injection of PPV was performed through a cannula placed into the femoral vein. Intra-arterial injection was through the vertebral cannula. For cisternal infusion, the dogs were tilted tail up and 2 ml of diluted PPV was injected slowly following removal of the same amount of cerebrospinal fluid. The dogs were kept in the tilted position for ten minutes.

1Research Fellow, 2Associate Professor, 3Clinical Fellow, 4Research Assistant, Department of Neurosurgery, Harvard Medical School and Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts, 02115.
6Ketamine Hydrochloride, Bristol Laboratories, Syracuse, New York.
The effect of PPV on normal vessels. A: Normal vertebral angiogram. B: Ten minutes after 15 mg PPV injection into the cisterna magna—17% vasodilatation is seen. C: Forty minutes later—further dilatation.

TABLE 1
Response of Basilar Artery Spasm to Administration of 15 mg Papaverine

<table>
<thead>
<tr>
<th>Dog #</th>
<th>Dose (mg kg)</th>
<th>Maximum vessel change (%)</th>
<th>Total</th>
<th>Time of maximum change</th>
<th>Duration of effect (%)</th>
<th>Blood clot at basilar artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>10-20'</td>
<td>+ + +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>60-90'</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>&gt; 120'</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>30-45'</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>10-20'</td>
<td>+ +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>0-10'</td>
<td>+ +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>10-20'</td>
<td>+ +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>10-20'</td>
<td>+ +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>10-20'</td>
<td>+ +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10'</td>
<td>10-20'</td>
<td>+ +</td>
</tr>
</tbody>
</table>

Necropsy was performed two weeks after subarachnoid blood injection.

Angiography was performed 10, 20, 30, 45, 60, 90 and 120 minutes after the injection of PPV. Arterial blood samples for blood gas analysis were taken prior to each angiogram. Autopsy was carried out in most cases and the clot was examined macroscopically.

**Results**

**Papaverine in Normal Dogs**

*Intravenous Infusion*

Two dogs received intravenous PPV (15 mg) and angiograms were taken 10, 30, and 60
EFFECT OF PAPAVERINE ON CEREBRAL ARTERIAL SPASM

minutes later. None had any significant vasodilatation. However, respiratory rate increased by more than 30% and mild hyperpnea continued for about 30 minutes. Transient hypotension (10% to 20%) was noted, but subsided within ten minutes. Arterial blood gas concentrations were minimally affected.

Intra-arterial Injection
Two dogs received intra-arterial PPV through the vertebral cannula. The first angiogram was taken ten minutes after PPV injection and in both cases about 10% vasodilatation of the basilar arteries was present. The effect was transient and disappeared within 30 minutes. Hyperpnea with intra-arterial PPV was greater than with intravenous PPV. Transient hypotension (45%) developed immediately but subsided within ten minutes. At this time the average change in arterial blood gases was minimal.

The severity of hypotension caused by intravenous and intra-arterial injection of PPV was proportionate to the dosage and with increased PPV hypotension became prolonged, cardiac arrhythmia appeared and at 150 mg of PPV death occurred.

Cisternal Infusion
Two normal dogs received PPV (15 mg) in the cisterna magna and transient (30 minutes) basilar artery dilatation (approximately 15%) occurred without significant change of blood pressure. The change in blood gases with subarachnoid injection of PPV was also minimal. Serious hypotension with respiratory arrest occurred in one dog about 30 minutes later. The angiogram taken under this condition revealed "pan-vasodilatation" of the circle of Willis including the smaller branches (fig. 1).

PAPAVERINE AND CHRONIC BASILAR ARTERIAL SPASM
Chronic spasm was confirmed by angiography in 17 dogs which had received cisternal blood two days or four days before (table 1).

Intravenous PPV (15 mg)
Angiographical follow-up was performed for 60 minutes following intravenous PPV in two dogs with severe spasm (32% and 46%). No significant vasodilatation was seen. Transient hypotension and mild hyperpnea were noted.

Intra-arterial PPV (15 mg)
Seven dogs with prior 43% average vasoconstriction were studied. In each case vasodilatation (average 58%) occurred within ten minutes (fig. 2). In four dogs dilatation was to control size and in one the basilar artery was large than its control size (110%). Vasodilatation was transient, however, and the arteries resumed their narrow caliber within 20 to 30 minutes (table 1 and fig. 3).

Hypotension and hyperpnea were similar to that observed in control dogs. Blood gas and pH levels were minimally affected (table 2).

Cisternal PPV (15 mg)
In six dogs pre-existing vasoconstriction averaged 41%. Maximum dilatation was seen

![FIGURE 2](http://stroke.ahajournals.org/)

(Dog #20) Intra-arterial PPV injection. A: Control angiogram. B: Chronic vasospasm two days after cisternal blood injection. C: Ten minutes after intra-arterial PPV injection. Vasospasm disappeared almost completely. D: Thirty minutes later, arteries are narrower than control.

Stroke, Vol. 3, January-February 1972
within ten minutes in all but one dog (becoming maximal by 30 minutes in the latter) (table 1), and vessel size recovered to almost normal but subsided to the contracted state within 45 minutes (figs. 3 and 4). The average change in blood pressure and arterial blood gas at ten minutes after PPV injection is shown in table 2. One dog developed serious hypotension but responded well to intravenous injection of caffeine.

NECROPSY FINDINGS
Necropsy confirmed the presence of a variable degree of thrombus in the prepontine cistern. The size of the thrombus had no relation to the degree of vasodilatation with PPV whether given by the arterial or cisternal route. In this regard two dogs with cisternal PPV had thick clot around the basilar artery but recovered from 54% to 97% of the normal basilar artery diameter (table 1).

<table>
<thead>
<tr>
<th>Administration</th>
<th>BP (%)</th>
<th>Pac (%)</th>
<th>Pco2 (%)</th>
<th>pH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial injection</td>
<td>-2 ± 10</td>
<td>-1 ± 11</td>
<td>-5 ± 10</td>
<td>0 ± 0.3</td>
</tr>
<tr>
<td>Cisternal injection</td>
<td>+2 ± 7</td>
<td>+11 ± 20</td>
<td>-4 ± 7</td>
<td>+0.3 ± 1.0</td>
</tr>
</tbody>
</table>

FIGURE 3
Composite comparison of intra-arterial versus subarachnoid instillation of PPV in dogs with hemorrhagic vasospasm.

TABLE 2
Average Changes of Arterial Blood Pressure and Blood Gas at Ten Minutes Following PPV Administration
FIGURE 4

(Dog #23) Subarachnoid PPV injection. A: Control angiogram. B: Chronic vasospasm two days after cisternal blood injection. C, D, E, F: 10, 30, 60 and 120 minutes after 15 mg PPV injection into the cisterna magna. Vasospasm has completely disappeared and the arteries show continuous dilatation for 60 minutes. At 120 minutes they again are constricted to the same degree as before.

Discussion

Papaverine is an alkaloid of the opium group and its primary pharmacological effect is the attenuation of smooth muscle contraction. Because of its ability to dilate arteries, papaverine had been proposed for the treatment of a number of illnesses associated with inadequate blood flow. Russek and Zohman reported that papaverine administered orally was effective in preventing the recurrence of seizures from vascular encephalopathy. Meyer et al. reported temporary clinical improvement in patients with ischemic infarction and demonstrated transient increase in brain oxygenation. Häggendal, using the 85 Kr clearance method, found a marked increase in cerebral blood flow and decrease of cerebral vascular resistance with papaverine administered intravenously. He added that papaverine reduced mean arterial blood pressure slightly.
for a few minutes, whereas the dilating effect on the cerebral vessels was obvious for at least one hour. Morello and his colleagues\textsuperscript{10} reported that intracarotid injection of papaverine in patients with no intracranial disease invariably caused arteriographical evidence of cerebral vasodilatation; also a single intravenous injection or continuous intravenous infusion of papaverine was effective in most instances. He also mentioned that the vasodilating effect was proportional to the dosage. Vasodilatation was observed by Huber and Handa\textsuperscript{11} following injection of 30 mg of papaverine into the carotid artery of patients without any disease of the central nervous system. The smaller arteries were affected significantly and dilated about 22.7\% with a considerable decrease of mean cerebral circulation time. Intravenous injection of 40 mg of papaverine had significantly less effect.

Jayne and his colleagues\textsuperscript{12} found that 120 mg of intravenous papaverine in a normal man would, in 20 minutes, increase cerebral blood flow 13\% as measured by the Kety-Schmidt method. The same was reported by Aizawa et al.\textsuperscript{18} McHenry and his colleagues\textsuperscript{6} reported that intravenous papaverine in seven patients with focal intracranial vascular lesions produced an 18\% increase in mean cerebral blood flow and a significant increase in regional blood flow over the ischemic area. Topical PPV also has been effective in relieving experimental cerebral vasospasm. Lende\textsuperscript{14} examined the topical effect of various drugs on local cerebral arterial spasm produced by mechanical or electrical stimuli in small animals and PPV was effective. Gurdjian and Thomas\textsuperscript{15} observed a similar effect in monkeys. Karlsberg et al.\textsuperscript{10} observed that cerebral vasoconstriction produced by prior intracarotid infusion of serotonin was relieved by the intracarotid infusion of histamine, isoxsuprine or PPV.

Recently, Kapp and Mahaley\textsuperscript{2,3} studied the effect of various drugs on blood-induced vasospasm on the basilar artery of the cat. They found that the most effective agents were choline, magnesium sulfate, papaverine and isosorbide dinitrate, in that order, when given intravenously. But they also noted that those drugs should be ranked in the reverse order with respect to safety. Fraser et al.\textsuperscript{1} produced hemorrhagic vasospasm in the basilar and vertebral arteries of the monkey. Topical application of phenoxybenzamine, a long-acting alpha-adrenergic blocking agent, was effective in preventing or reversing such blood-induced acute vasospasm. They felt that the vasodilator effect was irreversible, although no mention was made about the period of observation. From catecholamine fluorescent studies, they concluded that blood-induced vasospasm was the result of a constrictor substance contained in blood that is functionally active at the alpha adrenergic receptor site of smooth muscle.

Our experimental method was designed to simulate as closely as possible the spasm associated with subarachnoid hemorrhage and intracranial aneurysm. This experimentally induced chronic vasospasm was not affected by small changes in other parameters such as blood pressure and arterial blood gas concentrations.

Intravenous injection had no vasodilator effect at the dosage of 15 mg (1.0 or 1.7 mg/kg). Intra-arterial injection was effective but transient, and subarachnoid injection was more effective and longer acting. The serious side effect of PPV was hypotension by whatever route of administration.

The fact that papaverine was effective by subarachnoid injection suggests that this agent was able by some means to reach the wall of the blood vessels despite the presence of the blood clot surrounding the wall of the basilar artery.

From the clinical standpoint an important consideration is the route of administration of any drug. Unfortunately agents that appear to be able to attenuate the constriction of cerebral arteries when given in sufficient doses systematically also induce severe hypotension. Intra-arterial injection obviously appears to be superior to intravenous injection but the result is fleeting and would require some method of continuous infusion. The serious risk of embolism with continuous intracarotid infusion diminishes the advocacy of that route. Topical application, at least experimentally, appears to be more effective but is probably less practical. The application of PPV to narrowed vessels at the time of operation for cerebral aneurysm would be of negligible long-term value. However, at the time of operation the placement of a small catheter with a small subcutaneous reservoir in the vicinity of major vessels for later introduction of a drug such as...
EFFECT OF PAPAVERINE ON CEREBRAL ARTERIAL SPASM

Papaverine if required might be a feasible adjunct in aneurysm surgery.

The treatment of spasm by present-day pharmacological agents that act directly on smooth muscle or impair the normal mechanisms for smooth muscle contraction such as papaverine or phenoxybenzamine is contraindicated because of hypotension. Future investigations should be directed at the precise mechanisms of spasm so that the pathogenic mechanism might be interrupted at its source.

Summary
The vasodilator effect of PPV on chronic hemorrhagic vasospasm in dogs was evaluated. Intravenous infusion was not effective. Intraarterial injection produced significant transient vasodilatation and moderate hypotension. Subarachnoid injection of PPV was more effective.

References
Papaverine Hydrochloride and Experimental Hemorrhagic Cerebral Arterial Spasm
Akio Kuwayama, Nicholas T. Zervas, Akira Shintani and Kenneth S. Pickren

Stroke. 1972;3:27-33
doi: 10.1161/01.STR.3.1.27
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1972 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/3/1/27

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/