Neurotoxicity of Intra-arterial Papaverine Preserved with Chlorobutanol Used for the Treatment of Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—Papaverine is used to vasodilate cerebral arteries undergoing vasospasm from subarachnoid hemorrhage. However, papaverine inhibits cellular respiration in vitro and could cause neurotoxicity in humans.

Methods—We studied 5 consecutive patients with cerebral vasospasm who were treated with intra-arterial papaverine preserved with chlorobutanol and imaged with MRI fluid-attenuated inversion recovery and diffusion-weighted imaging after treatment. One patient had histological analysis of the brain at autopsy.

Results—All 5 patients exhibited marked neurological decline immediately after treatment, and this was sustained through hospital discharge. In all cases, MRI images showed selective gray matter–only signal changes within the vascular territory treated with papaverine. Histological analysis of 1 case brought to autopsy showed selective injury to islands of neurons with relative sparing of white matter.

Conclusions—Intra-arterial delivery of papaverine preserved with chlorobutanol into vasospastic anterior cerebral arteries may result in marked neurological deterioration with selective gray matter changes on MRI imaging. This effect is consistent with a permanent toxic effect to human brain. It is unclear whether this toxicity is caused by papaverine or chlorobutanol, and its use in the treatment of cerebral vasospasm should be reserved for cases without alternatives.

Key Words: endovascular therapy ■ papaverine ■ subarachnoid hemorrhage ■ vasospasm

Cerebral vasospasm after subarachnoid hemorrhage may produce cerebral ischemia, causing neurological morbidity in 18% to 25% of patients with aneurysmal rupture. Vasospasm occurs predominately within large intracranial vessels, and typically begins after day 4 of subarachnoid hemorrhage with peak effect typically occurring 6 to 14 days after hemorrhage. Cerebral infarction can be prevented by dilating vasospastic vessels, either with balloon angioplasty or by infusing a vasodilator drug intra-arterially. Commonly used intra-arterial agents include papaverine and verapamil. Although a potent arterial vasodilator, the use of papaverine is tempered by its ability to increase intracranial pressure, and it has been reported to cause immediate neurological deterioration.

We report a new concern over the use of intra-arterial papaverine. We report a consecutive series of 5 patients with angiographic vasospasm who experienced both sustained neurological deterioration and gray matter changes imaged on MRI within the vascular territory of the papaverine infusion. Histological analysis confirms selective gray matter damage to these brain regions.

Methods

This is a retrospective review of 5 consecutive cases at 1 United States medical center treated between November 2002 and January 2003. After the identification of the first case, we performed MRI fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted brain imaging after intra-arterial papaverine usage in the subsequent 4 cases. This case series is consecutive and comprehensive; no patient treated with papaverine during this period was excluded. During this time period, our medical center treated 23 patients with aneurysmal subarachnoid hemorrhage.

The neurological status of each patient immediately preceding treatment of vasospasm was derived from hospital records. Glasgow coma scale assessments were abstracted from nursing records. The detailed treatment of each patient, including site and extent of angioplasty, papaverine infusion site and dose, and the results of diagnostic angiography, was reviewed by a neurointerventional neuroradiologist. Brain MRI images were reviewed by a neuroradiologist.

The decision to treat patients for vasospasm was made on the basis of clinical findings (cases 2, 3, and 4) or based on diagnostic studies of vascular narrowing (computed tomographic angiography in case 1 and rising transcranial Doppler velocities in case 5). Papaverine was supplied in 10 mL vials of 300 mg papaverine in solution, with 0.5% chlorobutanol as a preservative. This was diluted in normal saline.
Clinical Course, Neurological Status, and Treatment

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/gender/race</td>
<td>66/F/White</td>
<td>48/M/Hispanic</td>
<td>75/F/Asian</td>
<td>66/F/White</td>
<td>65/M/Hispanic</td>
</tr>
<tr>
<td>Presenting HH/Fisher</td>
<td>1/II</td>
<td>5/IV</td>
<td>1/IV</td>
<td>3/III</td>
<td>3/IV</td>
</tr>
<tr>
<td>Papaverine SAH day</td>
<td>6 and 7</td>
<td>9</td>
<td>3</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Pre/papaverine GCS</td>
<td>E4M6V5</td>
<td>E4M6V4</td>
<td>E4M6V2</td>
<td>E4M6V5</td>
<td>E4M6V5</td>
</tr>
<tr>
<td>Postpapaverine GCS</td>
<td>E4MSV</td>
<td>E2MSV</td>
<td>E4MSV2</td>
<td>E3M4V</td>
<td>E1M4V</td>
</tr>
<tr>
<td>Neurological examination prepapaverine</td>
<td>Normal except extensor plantar responses bilaterally</td>
<td>Sleepy, oriented, moved extremities voluntarily except left leg withdrawal to pain only</td>
<td>Eyes open to voice, follows some commands only, no motor deficit</td>
<td>Somnolent, disoriented, no motor deficit</td>
<td>Normal</td>
</tr>
<tr>
<td>Neurological postpapaverine</td>
<td>Eyes closed, bilateral flexor posturing to pain (following second treatment)</td>
<td>Eyes closed, follows no commands, localized pain with both arms but not legs</td>
<td>Eyes open, global aphasia, moderate right hemiparesis</td>
<td>Eyes open spontaneously, global aphasia, no spontaneous movements, withdraws right arm only to pain</td>
<td>Eyes closed, unresponsive to voice, flexes arms, triple-flexion legs</td>
</tr>
<tr>
<td>Aneurysm treated</td>
<td>Supraclinoid</td>
<td>Acom</td>
<td>Acom</td>
<td>Supraclinoid</td>
<td>Carotid and MCA</td>
</tr>
<tr>
<td>MRI done SAH day</td>
<td>10</td>
<td>13</td>
<td>18</td>
<td>8 and 10</td>
<td>10</td>
</tr>
<tr>
<td>MRI Changes</td>
<td>Bilateral mesial frontal lobe</td>
<td>Bilateral mesial frontal lobe</td>
<td>Left mesial frontal lobe</td>
<td>Right mesial frontal lobe</td>
<td>Bilateral mesial frontal lobe</td>
</tr>
<tr>
<td>Vessel(s) treated with papaverine</td>
<td>Bilateral ACA twice</td>
<td>Bilateral ACA</td>
<td>Left ACA</td>
<td>Right ACA</td>
<td>Bilateral ACA</td>
</tr>
<tr>
<td>Papaverine dose</td>
<td>400 and 300 mg</td>
<td>450 mg</td>
<td>200 mg</td>
<td>200 mg</td>
<td>263 mg</td>
</tr>
</tbody>
</table>

HH indicates Hunt Hess grade; Fisher, Fisher group; GCS, Glasgow coma scale; Acom, anterior communicating artery; ACA, anterior cerebral artery; SAH, subarachnoid hemorrhage; SAH day, day number following SAH; and MCA, middle cerebral artery.

without heparin, to a concentration of 3 mg/mL papaverine and 0.05% chlorobutanol, and this solution was infused through a 0.014 in microcatheter (Cordis Prowler 14) or 0.018 in microcatheter (Cordis Prowler) typically no faster than 10 mg/min (3 to 4 mL/min) using hand injection. For direct anterior cerebral artery (ACA) infusions, the microcatheter was placed immediately distal to the origin of the ACA. Contrast was not added to the diluted papaverine and in no cases were papaverine crystals seen in the solution.

One patient expired because of poor neurological status, and a brain autopsy was performed. Coronal sections of the brain were made at the level of the caudate head, thalamus, and atria of the lateral ventricle, and tissue was examined inside and outside regions shown as abnormal on brain imaging. Tissue was stained with hematoxylin and eosin, and selective sections were stained with anti–CD-68 to identify activated macrophages and microglia. The histology was reviewed by a neuropathologist.

**Results**

Five consecutive patients during a 3-month period required intra-arterial papaverine for the treatment of angiographic or clinical vasospasm, and had MRI imaging of the brain after treatment. The demographic and clinical characteristics of each patient are shown in Table 1, and representative FLAIR and diffusion-weighted images of the brain are shown for each case in Figure 1.

Each patient had a marked change in neurological status immediately after endovascular treatment, as evidenced by the neurological examination and Glasgow coma scale scores off sedation. Each of the 5 patients had a sustained change in neurological examination through hospital discharge. One patient (case 1) received papaverine on 2 occasions separated by 1 day, and experienced clinical decline after each treatment. MRI imaging performed between 1 and 13 days after vasospasm treatment showed changes in all patients, most notably cases 1, 3, and 5. The changes are best seen on diffusion-weighted images, and on FLAIR images the bright signal was restricted to gray matter. Apparent diffusion coefficient maps showed reduction in areas appearing bright on diffusion-weighted images.

The absence of abnormal signal within white matter raised the question of selective gray matter toxicity, rather than ischemic infarction produced by the vasospasm process. This observation in case 1 led to MRI imaging in the subsequent 4 cases as part of our quality improvement process. Case 4 had a preprocedure MRI as well. Papaverine was administered to both ACAs in cases 1, 2, and 5 (Figure 1A, 1B, and 1E), into the left ACA of case 3 (Figure 1C), and into the right ACA of case 4 (Figure 1D); MRI changes appear only within the regions treated with papaverine. Case 4 had a preprocedure MRI that did not show right ACA diffusion or T2 signal changes. Additional papaverine was infused into the supraclinoid internal carotid artery after supraclinoid and middle cerebral artery (MCA) angioplasty on the right in case 2, and into both supraclinoid arteries after bilateral supraclinoid and MCA angioplasty in case 5. A transient embolic occlusion of a right MCA branch occurred in case 5 during the procedure.

Patient 5 expired 7 days after vasospasm treatment by withdrawal of medical support. Grossly, the brain had one area of softening near the parietal-occipital junction in the interhemispheric fissures of the right hemisphere consistent with the embolic event occurring during angiography. Histological analysis of the brain at the section shown by white line in Figure 1E is shown in Figure 2. Hematoxylin and eosin stains of cortex revealed scattered regions of eosinophilic neurons intermixed with healthy appearing neurons and no coagulation necrosis (Figure 2A). White
matter appeared pale with some vacuolization tissue (Figure 2E). Anti–CD-68 stains for macrophages and microglia showed marked staining of macrophage within the abnormal gray matter (Figure 2C) and relative lack of staining of microglia within white matter from the same region (Figure 2F). Similar analysis of the frontal lobe far left lateral in the same coronal section, within normal-appearing brain by MRI, showed no cellular damage or activation of macrophages on CD-68 staining (Figure 2B and 2D). These findings are most consistent with either a direct toxic effect on neurons or laminar necrosis occurring 5 to 7 days earlier.

Figure 2. Histology of case 5 taken from coronal brain slices indicated by the white line in Figure 1E. A, Hematoxylin and eosin (H&E) stain of the medial frontal gray matter revealing isolated islands of eosinophilic neurons without coagulation necrosis. There were moderate reactive changes within capillaries. B, H&E stain of the lateral frontal gray matter showing no ischemic neurons and normal capillaries. C, Anti–CD-68 stain from the medial frontal gray matter showing marked staining of reactive microglia consistent with a 5- to 7-day-old injury to gray matter. D, Anti–CD-68 stain from lateral frontal gray matter showing few reactive microglia. E, H&E stain of white matter from the medial frontal lobe revealing some vacuolization but otherwise normal white matter and (F) lack of significant microglia activation on CD-68 staining from the same region. These changes are consistent with a toxic effect primarily to gray matter. Bar length in A is 50 μm for A, B, and E, and 100 μm for C, D, and F.

The papaverine used came from 2 different lots; both lots were returned to the 2 suppliers of the drug. No prior adverse events of this type had been reported and no concern over the manufacturing process was reported.

Discussion

We present 5 consecutive cases treated with intra-arterial papaverine preserved with 0.5% chlorobutanol in which each patient experienced a sustained marked decline in neurological status with accompanying changes on MRI imaging corresponding to the locations of brain exposed to papaverine. Brain histological analysis of 1 case revealed changes not consistent with ischemic infarction, but rather changes consistent with a direct neurotoxic effect or laminar necrosis as can be seen in global circulatory failure.

These changes may represent a direct neurotoxic effect of papaverine and less likely from chlorobutanol. Papaverine blocks complex I and NADH-linked mitochondrial respiration,11 depolarizes mitochondria directly,12 and may inhibit specific dehydrogenase in the Krebs cycle.13 An agent that blocks mitochondrial respiration would be expected to produce neurotoxicity similar to hypoglycemia consistent with what was seen histologically in case 5; it has also been reported to cause seizure.14 Papaverine can open the blood brain barrier15 and at concentrations exceeding 0.4% can be directly toxic to rabbit endothelial cells.16 The drug presumably crosses the blood-brain barrier at a rate dependent on concentration, transit time, and the degree of blood-brain barrier compromise. In the
setting of vasospasm, cerebral transit time will be increased, increasing the absorption of papaverine into cerebral tissue. The lack of MRI changes within the middle cerebral territories in cases 2 and 5 could be accounted for by a short cerebral transit time resultant from prior MCA angioplasty. Therefore, vessels in which blood flow is slow may be particularly susceptible to papaverine toxicity. Additional clinical evidence of papaverine toxicity is the striking direct correlation between the brain region injured and the arterial distribution irrigated with papaverine; with the exception of the MCA regions that had been treated with prior angioplasty, the correlation between treated vessel and MRI changes was 1-to-1. Finally, these changes were seen in consecutive cases making a chance association unlikely.

Alternatively, the preservative chlorobutanol may have been responsible for these changes. Chlorobutanol is widely used as a preservative for pharmaceuticals and was a component of the papaverine solution administered to our 5 patients. Although little has been reported about toxicity of this agent, it does appear to produce dose-dependent reversible sedation in humans. Neurotoxicity of chlorobutanol has been reported after intrahectatic injection of 0.05% chlorobutanol in rabbit models, raising caution for intrahectatic injection of any substance preserved with chlorobutanol. We are unaware of any reported cases of neurotoxicity in animals or humans after intra-arterial administration of this agent. Even though it remains unclear if administration of preservative-free papaverine would have mitigated the toxicity we observed, it seems prudent to avoid papaverine preserved with chlorobutanol.

It is possible that some other aspects of the treatment other than papaverine infusion are responsible for the observed neurological deterioration and MRI changes. A low-flow state produced by relative hypotension in the setting of spasm could be implicated. However, no significant decline in systemic blood pressure was observed in the intensive care unit or during anesthesia in all cases; all patients were hypertensive during this time, and 3 of 5 patients were treated with arterial pressors for the mitigation of clinical vasospasm. Because the neurological deterioration was noted immediately after papaverine infusion in all 5 consecutive cases, and there was no evidence of hemodynamic instability during the procedure, we feel that the observed neurological deterioration is unlikely related to the anesthesia process. Alternately, transient vascular occlusion with the microcatheter during the instillation of papaverine could have produced brain infarction. However, the microcatheter used for instillation of papaverine was smaller than the vascular lumen of the treated vessel in all cases, so adequate flow around the catheter was allowed during infusion, and the pathology is not consistent with infarction. Although histological analysis of the abnormal gray matter in case 5 could be interpreted as laminar necrosis as would be seen in global ischemia, the absence of white matter pathology argues against a low-flow state causing these changes. Laminar necrosis is seen typically when blood flow is completely eliminated (global ischemia) and typically not seen in cases of focal ischemia.

Finally, we do not believe that the drug infused was contaminated by some unknown substance, because the lots of papaverine used in these cases were not all the same, and the drug came from 2 different manufacturers.

Our report is the first case series to our knowledge suggesting neurotoxicity from the drug in humans; however, other case reports of papaverine toxicity have appeared. Papaverine has been reported to cause abrupt loss of consciousness in some patients, reversible brain stem depression if infused in the posterior circulation, and transient blindness if infused into the ophthalmic artery. However, given the >2-decade experience with papaverine we have not found other MRI based reports suggesting neurotoxicity of the drug. It is possible that this toxic effect could have been missed because MRI imaging after intra-arterial papaverine is not routine. Additionally, in many centers, papaverine is not used unless patients are markedly symptomatic from spasm, and therefore further neurological deterioration would be difficult to appreciate. MRI images obtained after such treatment could easily have been misinterpreted as showing infarction. Clinical deterioration would likely be attributed to the vasospasm itself rather than the drug. Therefore, it is possible this effect is underrecognized and underreported.

We conclude that papaverine may directly damage brain when infused into the ACA distribution in humans, likely by a neuronal toxic effect, and we recommend that alternative drugs like verapamil be used for treating vasospasm not amenable to angioplasty.

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