Paradoxical aggravation of vasospasm with papaverine infusion following aneurysmal subarachnoid hemorrhage

Case report

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Reports of intraarterial papaverine infusion as treatment for cerebral vasospasm are few and documented complications are uncommon. The authors report the case of a patient with paradoxical aggravation of cerebral arterial narrowing during selective intraarterial papaverine infusion intended to treat vasospasm following aneurysmal subarachnoid hemorrhage (SAH). A 48-year-old man presented to the authors’ service with symptomatic vasospasm 10 days after experiencing an SAH. The ruptured anterior communicating artery aneurysm was surgically obliterated the following day, and thereafter maximum hypervolemic and hypertensive therapies were used. However, the patient remained lethargic, and a stable xenon–computed tomography (CT) cerebral blood flow (CBF) study revealed CBF to be 15 cc/100 g/minute in the left anterior cerebral artery (ACA) and 25 cc/100 g/minute in the right ACA territories. Cerebral arteriography demonstrated diffuse severe left ACA and mild left middle cerebral artery (MCA) vasospasm. In response intraarterial papaverine was infused into the internal carotid artery just proximal to the ophthalmic artery. During the infusion the patient became aphasic and exhibited right hemiplegia. Arteriography performed immediately after the intraarterial papaverine infusion revealed diffuse exacerbation of vasospasm in the distal ACA and MCA territories. A repeat xenon–CT CBF study showed that CBF in the left ACA and the MCA had drastically decreased (2 cc/100 g/minute and 10 cc/100 g/minute, respectively). Despite aggressive management, infarction ultimately developed.

This is the first clinical case to illustrate a paradoxical effect of intraarterial papaverine treatment for vasospasm following aneurysmal SAH. The possible mechanisms of this paradoxical response and potential therapeutic reactions are reviewed.

Key Words • cerebral vasospasm • papaverine • subarachnoid hemorrhage • drug reaction • angiography

Cerebral vasospasm remains a leading cause of morbidity and mortality following aneurysmal subarachnoid hemorrhage (SAH). Recent advances, including early surgery,19,20,35,40 hypervolemic3,18,31,38,45 and hypertensive therapies,3,7,18,21 and nimodipine administration,1,12,43 have reduced the incidence of symptomatic vasospasm. More aggressive endovascular interventions have been reserved for refractory vasospasm. Balloon angioplasty may be effective for larger proximal arteries,4,9 however, it cannot be applied to small-caliber distal cerebral vessels or severely narrowed spastic segments. Experimental use of intraarterial papaverine for cerebral vasospasm was first reported in the 1970s.2,3

Since the initial reports of selective intraarterial cerebral papaverine infusion in humans, published by Kassell, et al.,17 and Kaku, et al.,16 a total of 67 patients have reportedly been treated with this agent for cerebral vasospasm following aneurysmal SAH.3,8,15,17,24,26,29,33,46

Only 10 complications have been recorded in these 67 patients: transient decreased mental status with hemiparesis (one patient),17 transient brainstem depression (four patients),3,26 seizure,5 monocular blindness secondary to orbital infarction,8 thrombocytopenia,33 bradycardia/heart block,29 and parenchymal hemorrhage (one patient each).29 None of these complications was attributed to aggravated vasospasm. In addition, two patients had ipsilateral pupillary dilation, which may represent a transient direct action of papaverine on pupillary smooth muscle.37

Jin and colleagues14 recently reported a dose-dependent aggravation of phorbol dibutyrate–induced microvascular constriction in vitro in rat brain slices with papaverine. Aggravated microvascular vasospasm following papaverine infusion may explain the common observation of a lack of correlation between angiographic and clinical benefit after intraarterial papaverine infusion.8,14,17 The present case represents a possible clinical correlate to those laboratory and clinical findings in which intraarterial papaverine treatment may lead to a paradoxical aggravation of vasospasm following SAH.
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![Fig. 1](left: Coronal T₁-weighted magnetic resonance (MR) image on postbleed Day 9 displaying subacute interhemispheric blood. Right: Coronal MR angiogram showing anterior communicating artery aneurysm and interhemispheric blood.)

Case Report

This 48-year-old right-handed man with a history of alcohol abuse presented to a community emergency department with a sudden severe headache, transient loss of consciousness, and epileptiform movements. No computerized tomography (CT) scan or lumbar puncture was performed on initial evaluation and the episode was attributed to alcohol intoxication. The patient was discharged home and remained lethargic. Nine days after the initial event he developed urinary incontinence and right leg weakness. On return to the emergency department he demonstrated right leg paresis and a right pronator drift with no cranial nerve deficits. A CT scan was reported to be normal and lumbar puncture was performed. Xanthochromia was present and the cerebrospinal fluid contained 4200 red blood cells and 92 white blood cells per high-power field. The patient was admitted to a medical service and magnetic resonance (MR) imaging was obtained, which demonstrated an anterior communicating artery (ACoA) aneurysm surrounded by interhemispheric blood (Fig. 1) and an established small medial left frontal infarct. The following day, 10 days after the initial ictus, cerebral angiography further delineated the ACoA aneurysm and demonstrated severe vasospasm involving both A1 branches (Fig. 2).

Examination and Preliminary Treatment. The patient was transferred to our neurosurgical service. He awoke easily to voice, was oriented, and paretic on the right side with 4/5 motor strength. To facilitate aggressive vasospasm management and protect the patient from further rebleeding, the decision was made to perform surgery, which resulted in clip obliteration of the ACoA aneurysm 11 days after the initial event. After the operation the patient remained intubated, but was awake, followed commands, and had 4/5 right motor strength, unchanged from preoperative status. An immediate postoperative xenon–CT cerebral blood flow (CBF) study was performed to assess perfusion in light of the patient’s significant preoperative vasospasm. This study showed greater hypoperfusion in the left than in the right ACA territories (10 cc/100 g/minute and 18 cc/100 g/minute, respectively, calculated by averaging all regions of interest in the ACA territory on three CT slices). Hypervolemic and hypertensive therapies were maximally advanced and a repeat xenon–CT CBF study made 4 hours later showed modest, though inadequate, augmentation of CBF in the left (15 cc/100 g/minute) and right (25 cc/100 g/minute) distal ACA territories (Fig. 3 center).

The patient underwent angiography, which showed persistent vasospasm (Fig. 4 left). The patient’s ongoing neurological deficit, which was associated with quantitative CBF reduction and corresponding cerebral vasospasm, led to the decision to initiate endovascular treatment.

Papaverine Infusion. A Tracker 18 microcatheter was introduced through a base catheter and a guidewire was advanced easily into the left A1 segment. However, multiple attempts at selective catheterization of the left ACA with various wires and catheters were unsuccessful and, therefore, papaverine was instilled by constant infusion into the internal carotid artery (ICA) just proximal to the ophthalmic artery. Although no systemic heparin administration was used, small amounts of 6000 U/L heparin flush were slowly infused through the base catheter. No heparin was infused through the Tracker microcatheter. After 25 minutes of constant infusion of 300 mg papaverine (0.3%) and 100 cc normal saline at 4 cc/minute (300 mg total), the patient became aphasic and exhibited right hemiplegia.

Postinfusion Examination. Papaverine infusion was stopped and immediate repeat angiography showed that, although vasodilation of the supraclinoid ICA, and A1 and M1 segments was achieved, new severe distal left middle cerebral artery (MCA) vasospasm had developed (Fig. 4 center and right). No alternative intraarterial dilating agents were used, in part because they were not immediately available and also because in our experience nitroglycerin infusions for vasospasm had not been effective in previously treated patients. An immediate xenon–CT CBF study demonstrated severe hypoperfusion in the left ACA (2 cc/100 g/minute) and MCA (10 cc/100 g/minute) distributions (Fig. 3 lower), although CT scans showed no infarction (Fig. 3 upper). Despite aggressive medical therapies, a subsequent CT scan confirmed the development of infarction in the left ACA and MCA territories (Fig. 5). The patient made no recovery from his deficits and was later transferred to a nursing care facility.

Discussion

Papaverine has long been known to relax smooth muscle in a nonspecific manner and has thus been used for its vasodilating capabilities. It is thought to act by inhibit- 

J. Neurosurg. / Volume 84 / April, 1996
ing phosphodiesterase and elevating intracellular levels of cyclic adenosine monophosphate. Papaverine was first used in neurological disease to treat ischemic occlusive cerebrovascular conditions, including stroke and hypertensive encephalopathy. Subsequent work focused on the potential benefits of using papaverine in treating vasospasm following aneurysmal SAH. To obtain a more potent local effect, early experimental studies utilized an intrathecal route of papaverine administration, in some cases using a sustained release preparation for longer effect. Others have used postoperative intrathecal–intracisternal papaverine. Recently, interest in papaverine has focused on selective intraarterial infusions in the acute management of vasospasm after less aggressive

![Fig. 3. Plain computerized tomography (CT) scans obtained after papaverine infusion (upper), prepapaverine stable xenon–CT cerebral blood flow map (center), and immediate postpapaverine blood flow map (lower). Scale is cc/100 g/minute. Average blood flow in a given vascular territory was calculated by averaging the flow values for all regions of interest in a given vascular territory over all three scanning slices. Prepapaverine blood flow values are 15 cc/100 g/minute in the left and 25 cc/100 g/minute in the right anterior cerebral arteries (ACAs); postpapaverine blood flows are 2 cc/100 g/minute in the left ACA and 10 cc/100 g/minute in the middle cerebral artery.](image-url)
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Therapies have failed. To date, only four series with 10 or more patients and several small series or case reports have been published. In total, 67 cases have been reported with 10 complications (Table 1). This excludes two patients with ipsilateral pupillary dilation, which is probably a direct effect of papaverine on pupillary smooth muscle.

The present finding of paradoxical aggravation of vasospasm during intraarterial papaverine treatment has not previously been reported. However, the complications that have been reported—brainstem depression following verteobasilar infusions, seizures, monocular blindness, and hemiparesis with decreased mental status—may have occurred as a result of aggravated vasospasm (Table 1). Four of these patients underwent immediate arteriography after exhibiting the complication (one patient with monocular blindness and three with brainstem depression); the arteriograms showed no exacerbated vasospasm. Three other patients did not have immediate follow-up arteriography, leaving the possibility of exacerbated vasospasm in those cases unresolved. However, even if postpapaverine arteriography is performed, the possibility of aggravated vasospasm in small distal vessels below the resolution of angiography cannot be excluded. Recent in vitro experiments indicate that paradoxical vasoconstriction as a response to papaverine infusion may occur in microvessels after activation of protein kinase C. The activation of protein kinase C is thought to mediate vasoconstriction in chronic vasospasm following aneurysmal SAH, and in a study by Jin, et al., papaverine was found to elicit a dose-dependent exacerbation of protein kinase C-induced vasospasm in the microvessels. The present case represents the first evidence that papaverine-induced vasoconstriction may also occur in larger distal vessels (Fig. 4 center and right).

Papaverine has also been used extensively in other systemic vascular beds for problems such as coronary spasm and impotence. An exhaustive literature review yielded no references to a paradoxical vasoconstrictive action of papaverine in these or other vascular beds. However, the cerebral circulation is unique in its reaction to drugs and exposure to aneurysmal SAH. For example, it is difficult to explain the lack of clinical benefit in patients with cerebral vasospasm that responds angiographically with vasodilation following intraarterial papaverine treatment. Kassell, et al., reported that 60% of patients treated with papaverine who had angiographic improvement in vasospasm had no clinical benefit, and Clouston, et al., noted that 50% of patients had no clinical benefit despite angiographic improvement. A more recent study demonstrated that only 52% of patients had objective clinical improvement despite a 76% rate of angiographic improvement. Although some of the patients in these cases may have sustained an irreversible ischemic injury prior to papaverine administration, these clinical and experimental findings indicate a possible paradoxical effect of papaverine at the microvascular level, which may account for the lack of ischemia reversal despite successful large vessel vasodilation.

Other potential etiologies of vasoconstriction during selective intraarterial papaverine treatment must also be considered. Coronary vasospasm has been reported in two patients following contrast infusion during cardiac angiography. This is an unusual finding and has been at least partially attributed to an anaphylactoid reaction with release of histamine, because both patients demonstrated systemic signs of anaphylaxis, including urticaria and hy-
potension. Our patient did not exhibit allergic signs during angiography and the onset of his symptoms occurred only during the intraarterial papaverine treatment. It is also unlikely that contrast material aggravated vasospasm in our patient because he had undergone previous cerebral angiography on two occasions without sequelae. Studies of the effect of radiographic contrast material on peripheral and renal vessels indicate no arterial vasoconstrictive action exists in these vascular beds, and no cases of radiographic contrast–induced vasoconstriction in the cerebrovascular system have been reported during angiography. Therefore, it is unlikely that the aggravated vasospasm in this case was contrast related. It may be possible that preservatives mixed with the papaverine, rather than the papaverine itself, caused the distal vessel narrowing in our patient. Papaverine has one supplier (Eli Lilly and Company, Indianapolis, IN) and has only one preservative (edetate disodium, 0.005%) mixed with it. Because papaverine is only supplied in this form and because other reports of exacerbated vasospasm with papaverine do not exist, it is difficult to distinguish which substance may be the causative agent.

Precipitation of papaverine in solution may also account for some of the reported complications. An early report notes thrombotic occlusion of the subclavian artery after angiography using Isovue 370 followed by papaverine infusion. This was thought to be related to concomitant heparin use as noted in a subsequent letter. An in-depth study of the compatibility of papaverine with various solutions showed that the drug at high concentrations (3.0%) will crystallize with as little as 2000 U/L heparin, but at lower concentrations, such as those used in the cerebrovascular system (0.3%), does not crystallize even in 10,000 U/L heparin. No incompatibilities were found with contrast agents or saline. However, a fine layer of precipitate formed when 0.3% papaverine was added to serum, which rapidly dissolved as more serum was added. This indicates that papaverine should be infused slowly and at low concentrations (0.3% or less) to allow adequate dilution in serum and prevent precipitation. The precipitation risk was minimized in our patient by using a 0.3% papaverine solution at a slow infusion rate, which has been described by other authors without angiographically documented embolic events. Our postpapaverine cerebral angiogram demonstrates significant narrowing of the M1 branches without “cropping” secondary to distal embolic obstruction (Fig. 4 center and right). We believe that the significant M1 vessel narrowing in our patient represents vasospasm and is not consistent with embolic phenomena.

Finally, catheter-induced vascular spasm can also occur with cerebrovascular angiography or endovascular interventions. Flow-induced vascular relaxation has been demonstrated in several studies, with the mechanism probably involving second messengers and not simply physical forces. The introduction of microcatheters into distal branches in the cerebrovascular system is known to cause spasm in some patients and may be a result of decreased flow through these segments, which diminishes flow-induced relaxation. The aggravated vasospastic segments in the present case involved primarily distal MCA vessels that were never catheterized. Although the left ACA underwent repeated attempts at catheterization, no spasm around the region of the catheter tip in the ICA was seen on angiography (Fig. 4). It is unlikely that the catheter positioned in the ICA resulted in significant flow reduction. Therefore, the appearance of paradoxical aggravation of vasospasm in our patient was probably not flow related or due to catheter or flow-induced vasospasm.

Conclusions

Selective intraarterial papaverine infusion may be an effective treatment for vasospasm following aneurysmal SAH, although reports of the efficacy of this therapeutic modality are still few and reported complications uncommon. The papaverine-induced aggravation of vasospasm that we encountered has not been reported previously, and it may be the clinical correlate of microvascular vasoconstriction demonstrated in the laboratory. This mechanism may explain other previously reported complications as well as the preponderance of complications encountered in vertebrobasilar infusions in which very small microvascular territories control vital functions, which become clinically evident when compromised.

The absolute indications for use of intraarterial papaverine infusion have not been fully defined, although integration of clinical, quantitative CBF, and angiography data will aid in the selection of patients at greatest risk for subsequent infarction without further intervention. When distal cerebral vasospasm is present, beyond the reach of angioplasty catheters, intraarterial papaverine treatment is presently one of the few available alternative treatments of refractory vasospasm. Aggressive attempts at selective catheterization of affected territories should be undertaken to limit the amount of vascular territory exposed to potential complications of papaverine infusion. Intraarterial papaverine should be administered in dilute solutions at slow rates.

If adverse effects occur, cessation of infusion should be immediately followed by arteriography. Although no effective alternative treatment has been established, consideration of angiotensin and/or nitroglycerin infusions may be warranted, albeit not supported by clinical experience. Ideally, more effective and safer intraarterial agents will be developed for treatment of patients with refractory symptomatic vasospasm.

References

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