Transient Neurologic Events Associated with Intraarterial Papaverine Infusion for Subarachnoid Hemorrhage–Induced Vasospasm

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Summary: This report describes three patients who experienced transient neurologic events associated with intraarterial papaverine infusion in the vertebrobasilar system. Two of these involved respiratory depression and underscore the need for careful monitoring and, when required, cardiopulmonary support.

Index terms: Vasospasm; Drugs, reaction; Subarachnoid space, hemorrhage; Interventional neuroradiology, complications of; Iatrogenic disease or disorder

Vasospasm is commonly found with subarachnoid hemorrhage and markedly contributes to its associated morbidity and mortality. Methods to combat the deleterious effects of vasospasm include hypertensive, hypervolemic therapy (1), calcium channel blockade (2), and angioplasty (3–7). Additionally, intraarterial infusion of papaverine has been used in a relatively small number of patients with variable success (8, 9). The duration of effect of papaverine is often transient compared with angioplasty, but it retains its relative appeal because of the presumed safety of intraarterial papaverine infusion. The following report details three cases in which transient neurologic events were experienced during intraarterial papaverine infusion into the vertebrobasilar system.

Case Reports

Case 1

T.H. is a 52-year-old woman who presented for evaluation with a severe headache but no additional neurologic deficit. A computed tomographic (CT) scan revealed a subarachnoid hemorrhage, and a cerebral arteriogram showed a left posterior internal carotid artery aneurysm without vasospasm. The aneurysm was clipped on day 1 after bleeding without complications. The patient was placed on nimodipine, phenytoin (Dilantin), and dexamethasone. On day 4, she developed left gaze nystagmus. CT revealed an edematous cerebellum and effacement of basal cisterns without hydrocephalus. Transcranial Doppler revealed marked elevation from baseline consistent with vasospasm; hypertensive, hypervolemic therapy was begun. On day 6, the neurologic exam again changed, with the patient becoming drowsy but otherwise intact. An arteriogram revealed severe vasospasm involving the middle and distal basilar artery (above the anterior internal carotid artery) and proximal portions of the superior cerebellar and posterior cerebral arteries (Fig 1). No vasospasm in the anterior circulation was found. Intraarterial administration of papaverine was suggested.

After systemic heparinization, a Tracker 10 catheter (Target Therapeutics, Fremont, Calif) was advanced coaxially with the tip positioned just proximal to the anterior internal carotid artery origin. A mixture of 300 mg of papaverine (Lilly, Indianapolis, Ind) in 100 mL of normal saline was administered by constant infusion at a rate of 0.5 mL/min. After a total of 21 mg of papaverine was infused, the patient became agitated and had blurred vision. She progressed within minutes to obtundation without response to pain. The right pupil was dilated and unresponsive. Papaverine was discontinued, and an angiogram revealed no change from the preinfusion exam with no wedging of the microcatheter. The microcatheter was removed. The patient's oxygen saturation did drop slightly, but she maintained voluntary respiration, and there was no change in heart rhythm or blood pressure. The patient recovered to a preinfusion neurologic status within minutes and was amnestic to the event. A second angiogram was again unchanged. No additional papaverine was infused.

Case 2

C.B., a 51-year-old woman, was admitted for acute headache and neck pain. On physical examination the patient was somnolent but arousable to verbal stimulation and was oriented to person, place, and time. There were no other unusual neurologic findings. CT scan showed a small

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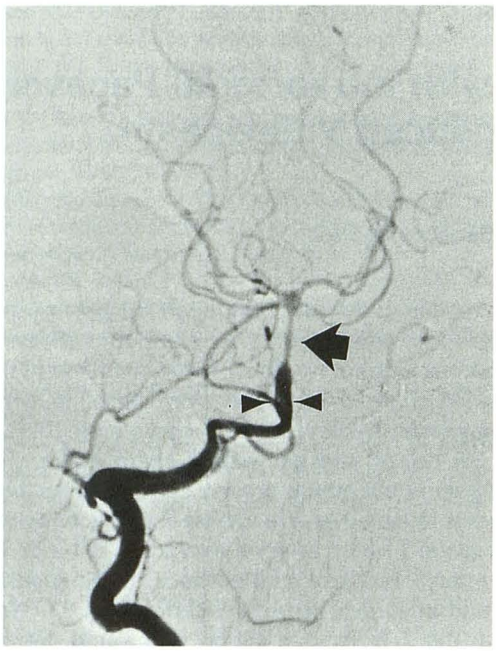

Fig 1. Severe vasospasm affecting the distal basilar artery after subarachnoid hemorrhage (*arrow*). The tip of the microcatheter is indicated by the *arrowheads*.

left superior ganglionic hemorrhage with intraventricular extension. Cerebral angiography revealed no obvious source of the hemorrhage. There was a small left ophthalmic aneurysm that was felt to be incidental and not related to the bleed and right subintimal dissection of the internal carotid artery, probably catheter related.

The patient became more lethargic 1 day after ictus. A ventriculostomy was placed for hydrocephalus.

Sequential transcranial Doppler over the next several days showed evidence of cerebral vasospasm in the anterior circulation for which the patient received hypertensive, hypervolemic therapy. Her neurologic status was unchanged in that she was arousable to verbal stimulation, followed commands, and was oriented to person, place, and time.

On day 11 after hemorrhage, the patient became lethargic and disoriented. She followed commands with all extremities with persistent verbal stimulation. Transcranial Doppler showed diffuse spasm in the anterior and posterior circulation. Cerebral vasodilatation was recommended in view of the deterioration of the patient's condition despite maximal medical treatment.

A cerebral arteriogram confirmed diffuse, severe spasm involving the distal vertebral arteries beginning just beyond the origin of the posterior internal carotid arteries, the basilar artery, and both posterior cerebral arteries. After systemic anticoagulation, a Tracker 18 catheter was positioned in the distal left vertebral artery, just proximal to the origin of the posterior internal carotid artery, through which a papaverine solution (300 mg in 110 mL of normal saline) was administered by constant infusion at 3 mL/min. Eight minutes after beginning the infusion, the patient had a respiratory arrest. Vital signs were otherwise stable except for a decrease in the systolic blood pressure from 200 to 160 mg Hg. The infusion was immediately stopped; an oral airway was placed; and the patient was ventilated with 100% oxygen in preparation of intubation. Respiration spontaneously resumed within 7 minutes. The procedure was terminated, and the patient was transferred back to the intensive care unit. CT scan showed no new findings.

Case 3

N.C. is a 45-year-old woman evaluated for the acute onset of headache followed by a seizure. When admitted to the emergency room, the patient was lethargic but arousable, moved all extremities, and had no cranial nerve deficits. CT revealed diffuse subarachnoid hemorrhage and early communicating hydrocephalus. An arteriogram failed to demonstrate an aneurysm or arteriovenous malformation. A persistent trigeminal artery was incidentally found. She was placed on nimodipine, phenytoin (Dilantin), and dexamethasone.

On day 4, the patient had a mild elevation of transcranial Doppler velocities but remained neurologically stable and intact. However, on day 6, she exhibited a decreased level of consciousness with mean transcranial Doppler velocities of 140 cm/sec (right) and 200 cm/sec (left). Another arteriogram demonstrated severe diffuse vasospasm and the presence of a left posterior communicating artery aneurysm. Angioplasty of the right middle cerebral artery was followed by slow, constant infusion of 300 mg of papaverine (300 mg/100 mL of normal saline) in the distal right internal carotid artery above the ophthalmic origin. This produced improved flow in both the right middle cerebral and anterior cerebral artery territories. Next a Tracker 18 catheter was positioned in the distal basilar artery above the level at the anterior internal carotid artery via the left trigeminal artery. Infusion of only 5 mg of papaverine (300 mg/100 mL of normal saline) in this location produced tonic eye deviation to the right and bilateral pupillary constriction that did not respond to light. The papaverine was stopped, and the patient returned to baseline within 2 minutes. The distal trigeminal and basilar arteries were successfully angioplastied. At the end of the procedure, the patient had stronger extremity movement in response to stimulation, but her level of consciousness had not changed.

Discussion

Subarachnoid hemorrhage from the rupture of an intracranial aneurysm occurs in approximately 26 000 Americans each year (10, 11). Cerebral vasospasm is the leading cause of morbidity and mortality in patients who survive aneurysmal subarachnoid hemorrhage, resulting in permanent neurologic deficit or death in 14% (11–13). Vasospasm is classified as either angiographic or clinical.

Angiographic vasospasm is defined as angiographic narrowing of at least one artery of the circle of Willis or its major branches. It is reported in up to 70% of patients after aneurysmal subarachnoid hemorrhage (10, 11). The vasospasm usually occurs between days 4 and 9 after hemorrhage (14–16).

Clinical vasospasm is characterized by the development of confusion and a decreased level of consciousness, followed by focal neurologic deficits. Clinical vasospasm temporally parallels angiographic vasospasm but occurs with less frequency, affecting only 20% to 30% of patients after subarachnoid hemorrhage (17).

Numerous methods have been tried to prevent or counteract cerebral vasospasm. These include medical (eg, hypertensive, hypervolemic therapy) (1), pharmacologic (eg, nimodipine) (2), and mechanical (eg, angioplasty) (3–7) regimens. The major thrust of medical and pharmacologic therapy is preventive; angioplasty is reserved for established, symptomatic vasospasm. Angioplasty has proved effective in reversing vasospasm in large, proximal cerebral vessels (3–7) but is not effective in reaching small, distal vessels. Also, complications such as vessel rupture or occlusion can result from angioplasty (5). Intraarterial papaverine recently has been reported as an alternative to angioplasty in patients with symptomatic vasospasm (8, 9).

Papaverine is an opium alkaloid that causes direct smooth muscle relaxation in arteries and arterioles diffusely (18). It is available in preparations for oral and intravenous administration, with (Lilly multidose vials) or without (Lilly ampuls) the preservative chlorobutanol. Papaverine has an average blood-level half-life of 0.8 hours (SD = 0.5) (19). Smooth muscle relaxation seems to be transient but is considerably longer than the half-life of papaverine in blood.

McHenry et al (20) demonstrated that both oral and intravenous papaverine increase regional cerebral blood flow in healthy humans, but the increase is modest, at best, and often transient. Cerebral intraarterial papaverine in the treatment of subarachnoid hemorrhage–associated vasospasm has been reported previously in a total of 25 patients (8, 9, 21, 22). Two transient neurologic events were experienced: (*a*) mental status changes and hemiparesis, and (*b*) pupillary dilatation. Both neurologic events resolved completely and occurred during infusions in the anterior circulation. Only 2 posterior territory infusions were described in these reports, and both were without adverse effect. An additional central nervous system complication of transient coma was noted after an intramuscular injection of papaverine by Ilan et al (23).

All of the neurologic events in this report occurred after intraarterial infusions of papaverine, with preservative, into the vertebral or basilar arteries. The resultant symptoms were related to brain stem dysfunction and were transient. The type and severity of symptoms seem related to the anatomic level of the papaverine infusion and possibly the degree of vasospasm. Obtundation and cranial nerve findings were present in all patients; however, apnea was noted only with the intraarterial infusion below the level of the anterior internal carotid artery.

The mechanism of action for these transient events is not, as yet, known. A direct pharmacologic effect of papaverine on the central nervous system seems most likely because of the short duration of symptoms and may be enhanced by the locally diminished cerebral blood flow secondary to vasospasm. Central nervous system depression has been noted as a side effect of papaverine use previously (24). The preservative chlorobutanol also might contribute to this effect. We could find no studies evaluating the potential for central nervous system change with intraarterial chlorobutanol alone. Alternatively, thromboembolic complications are possible from precipitate formation in this slow-flow state with various drug concentrations. Papaverine is known to precipitate with radiographic contrast (25–29), and a precipitate also may be seen at various papaverine concentrations and pH levels in serum and heparinized saline (30). A cardiovascular explanation seems unlikely, because these patients had no major changes in cardiac rhythm or blood pressure. However, arrhythmias and other conduction defects are known to be possible with papaverine administration (23, 24).

Transient neurologic changes occurred in 3 (50%) of 6 patients undergoing vertebrobasilar infusions in our series. The frequency seems higher in the vertebrobasilar territory compared with anterior circulation infusions, of which 2 (6.3%) of 32 had transient neurologic changes. Mydriasis is now known to be a common and insignificant occurrence with intraarterial infusion of papaverine in the anterior circulation near the ophthalmic origin and was, therefore, excluded (31). The incidence of neurologic

change may be directly related to the degree of spasm, concentration of papaverine, and number of perforating vessels in the infusion territory. Although the neurologic events were transient in all patients, those occurring in the posterior circulation seem more frequent and consequential. Therefore, one may elect to start with less-aggressive angioplasty in the posterior circulation, especially when spasm is severe or a low infusion location (below the anterior internal carotid artery) is required.

These transient neurologic events indicate that intraarterial infusion of papaverine for vasospasm is not a completely benign procedure. Patients need careful monitoring and neurologic evaluation during infusion. Intraarterial infusions in the posterior circulation carry the risk of brain stem dysfunction, and therefore, respiratory and cardiovascular support need to be available when this therapy is attempted.

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