Complications Associated with Intraarterial Administration of Papaverine for Vasospasm Following Subarachnoid Hemorrhage

—Two Case Reports—

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Abstract

Complications associated with intraarterial papaverine infusion occurred in two patients treated for vasospasm due to subarachnoid hemorrhage (SAH). A 42-year-old male with an anterior communicating artery aneurysm underwent craniotomy and aneurysm clipping. Five days after the SAH occurred, angiography demonstrated moderate vasospasm in spite of hypervolemic-hypertensive therapy. During papaverine infusion into the carotid artery, he suffered loss of consciousness due to a seizure for a few minutes. A 61-year-old female with a right internal carotid-posterior communicating artery aneurysm underwent clipping. Six days after the SAH occurred, angiography demonstrated severe vasospasm in spite of hypervolemic-hypertensive therapy. Angiography performed immediately after papaverine infusion into the carotid artery revealed exacerbation of the vasospasm. Finally she suffered cerebral infarction and died. Complications of intraarterial papaverine infusion are potentially dangerous. We recommend trial administration of papaverine with angiography and neurological examination before full dose infusion to avoid complications.

Key words: cerebral vasospasm, papaverine, subarachnoid hemorrhage, intraarterial injection

Introduction

Cerebral vasospasm remains a leading cause of morbidity and mortality following subarachnoid hemorrhage (SAH). Angioplasty and intraarterial administration of papaverine have recently been used as a definitive treatment for vasospasm. Papaverine relaxes smooth muscles in a nonspecific manner and thus is used for vasodilation. Papaverine was first used in neurological disease to treat ischemic occlusive cerebrovascular conditions, and subsequently for treating vasospasm following aneurysmal SAH. However, recent studies of the treatment of vasospasm due to SAH with intraarterial injection of papaverine have failed to confirm benefits. In addition, various complications have been reported due to intraarterial administration of papaverine. We describe the occurrence of seizure and aggravated vasospasm as complications of papaverine administration in patients with vasospasm.

Case Presentation

Case 1: A 42-year-old male with a history of hypertension suddenly suffered severe headache. Computed tomography (CT) revealed SAH of Hunt and Hess grade II. Angiography showed an anterior communicating artery (ACoA) aneurysm (Fig. 1 left). The ACoA aneurysm was immediately clipped and a cisternal drainage tube was inserted, which was removed 3 days later. Hypervolemic and hypertensive
Fig. 1 Case 1, a 42-year-old male. left: Left anteroposterior (AP) carotid angiogram on day 1 after subarachnoid hemorrhage, demonstrating an anterior communicating artery (ACoA) aneurysm (arrow). center: Left AP carotid angiogram on day 5 demonstrating vasospasm in the A2 segments of the bilateral anterior cerebral arteries (ACAs) and the M2 segment of the left middle cerebral artery (MCA). The ACoA aneurysm has been clipped. right: Left AP carotid angiogram after papaverine infusion demonstrating improvement of vasospasm in the ACAs and MCA.

Fig. 2 Case 2, a 61-year-old female. left: Right anteroposterior (AP) carotid angiogram on day 1 after subarachnoid hemorrhage, demonstrating an internal carotid artery aneurysm (arrow). center: Right AP carotid angiogram on day 6 demonstrating severe vasospasm in the right anterior and middle cerebral arteries. right: Right AP carotid angiogram after papaverine infusion demonstrating very slow circulation and no visualization of the distal portions of intracranial vessels.

therapies were given, but his consciousness deteriorated to somnolence 5 days later. Emergency angiography demonstrated moderate vasospasm in the A2 segments of the bilateral anterior cerebral arteries (ACAs) and the M2 segment of the left middle cerebral artery (MCA) (Fig. 1 center). A catheter for angiography was inserted proximal to the ophthalmic artery, and papaverine was intraarterially injected (papaverine 120 mg/100 ml of 0.9% NaCl, infusion rate 8 mg/min). After the administration of 30 mg of papaverine (about 27 ml of 0.9% NaCl), loss of consciousness for a few minutes and tonic posture were observed. These symptoms indicated a seizure attack. Repeat angiography re-
revealed that the vasospasm of the bilateral A2 segments and the left M2 segment had disappeared (Fig. 1 right). After the seizure, examination revealed no neurological abnormalities. The patient was discharged 25 days later.

Case 2: A 61-year-old female with a history of hypertension suddenly suffered severe headache. CT revealed SAH of Hunt and Hess grade III. The same day, emergency angiography indicated a left MCA aneurysm. Surgery through the left pterional approach was immediately performed, but no left MCA aneurysm was detected. The next day, angiography showed a right internal carotid-posterior communicating artery aneurysm (Fig. 2 left). Two days after the onset of SAH, the internal carotid-posterior communicating artery aneurysm was clipped through the right pterional approach. Hypervolemic and hypertensive therapies were given. Six days after the onset of SAH, increased blood pressure suddenly occurred. Angiography demonstrated severe vasospasm in the right MCA and ACA (Fig. 2 center), and moderate vasospasm in the left MCA. An angiographic catheter was inserted proximal to the ophthalmic artery, and papaverine was intraarterially injected (papaverine 300 mg/150 ml of 0.9% NaCl, infusion rate 9.1 mg/min). To evaluate the effect of papaverine, the infusion was stopped at 50 mg of papaverine (25 ml of 0.9% NaCl). Angiography immediately performed showed no dilatation of the right MCA. We thought that the effect of the papaverine was not adequate, and an additional 250 mg of papaverine was injected (300 mg total). Repeat angiography showed very slow circulation and almost no visualization of the right MCA and ACA (Fig. 2 right). Since the patient’s consciousness level deteriorated from II-10 (Japanese Coma Scale) to II-30, angiography was stopped. She showed further deterioration of consciousness and apnea. The next day, CT showed cerebral infarction in the right MCA and the bilateral ACA areas. The patient died 2 days after the last angiography.

Discussion

Various complications have been associated with papaverine infusion, including monocular blindness,21 seizures,21 brainstem dysfunction,18 focal neurological deficits that resolved on cessation of papaverine administration,6 formation of crystal emboli,8 and thrombocytopenia.13 Clinical seizure was observed in our Case 1, and aggravation of vasospasm in Case 2. Seizure due to papaverine infusion3,7 and paradoxical aggravation of vasospasm9 have both been reported. Papaverine may have a paradoxical effect at the microvascular level, which accounts for the lack of ischemic reversal despite successful large vessel vasodilation5 seen as a discrepancy between objective clinical and angiographical improvement. Paradoxical aggravation has been observed in the A2 and M2 portions of the ACA and MCA, and dilatation in the A1, M1, and M2 portions.19 The inside diameter seemed to be unchanged in the M1 portion of the MCA in Case 2, so paradoxical aggravation may have occurred in the more distal portion of the MCA. We think that the aggravation in Case 2 was not due to embolism, because emboli were not observed in the vessels of the right ACA and MCA.

Other potential etiologies of vasoconstriction during papaverine treatment include immuno-mediated reaction caused by papaverine or preservatives mixed with papaverine,19 and precipitation of papaverine in solution.3,20 However, our patients did not exhibit allergic signs or other systemic abnormal findings during the papaverine treatment, and the concentration and infusion rate of papaverine used in our cases were the same as those previously reported (0.3% concentration, 300 mg of papaverine was infused over 15 to 60 minutes).5,12 Since papaverine in 0.3% or greater concentration formed a precipitate when mixed with human serum,20 we think that the concentration of 0.3% is the limit for intraarterial injection. Although iopamidol was used as the radiological contrast medium in our cases, this material is not reported to form a precipitate with papaverine. The causes of these various complications remain unclear, but may be related to the ineffectiveness of the treatment in various patients.

Abuse of this treatment as currently being used is warranted. When papaverine infusion is performed as a trial, it is important to avoid these complications. Intubation of the patient and slow infusions with both arterial pressure and intracranial pressure monitoring have been advocated.6 However, in our cases and previously reported cases,3,4,6 papaverine treatment at a conventional concentration and infusion rate induced aggravation of vasospasm and brain stem depression. Respiratory depression was induced by 65 mg of papaverine (300 mg/110 ml of normal saline, infusion rate 8.2 mg/min) and 21 mg (300 mg/100 ml of normal saline, infusion rate 1.5 mg/min).6 Consciousness disturbance was induced by 100 mg of papaverine (infusion of 300 mg for over 30 min).11 In our cases, 30 mg and 50 mg of papaverine infusion caused complications. We recommend that trial administration of intraarterial papaverine be performed before full dose infusion. After trial administration, the absence of aggravation of vasospasm and neurological deterioration

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must be confirmed by immediate follow-up angiography and neurological examination. Angiography may also detect aggravation of circulation in the distal vessels or circulation time.

References


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