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Intraarterial Injection of Amrinone for Vasospasm Induced by Subarachnoid Hemorrhage

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Summary: We describe two patients who had cerebral vasospasm after subarachnoid hemorrhage that was refractory to intraarterial injection of papaverine. Both patients were successfully treated with intraarterial injection of amrinone after intraarterial injection of papaverine. It is suggested that intraarterial amrinone, which has a vasodilatory action, may be therapeutically useful for cerebral vasospasm.

Index terms: Vasospasm; Subarachnoid space, hemorrhage; Drugs, intraarterial injection

Intraarterial injection of papaverine for cerebral vasospasm after subarachnoid hemorrhage has been accepted as one of the appropriate treatments for this condition (1, 2); however, it does not always yield successful results. Intraarterial papaverine is not always effective, and, in some patients, arterial narrowing has recurred after successful treatment for cerebral vasospasm. The pathogenesis of cerebral vasospasm is unclear. It is thought to involve not only functional changes of the muscle contraction but also morphologic changes of the arterial wall. Successful clinical management of cerebral vasospasm by transluminal balloon angioplasty has been reported (3). This may support the idea that vessels affected by subarachnoid hemorrhage develop arterial stiffness due to morphologic changes (4). On the other hand, intraarterial infusion of vasodilative drugs has also been reported as appropriate treatment for cerebral vasospasm (1, 2). This may support the idea of derangement of the contraction-dilatation mechanism of smooth muscle after subarachnoid hemorrhage (5, 6). We report here the use of intraarterial amrinone in two patients with vasospasm that was refractory to papaverine injection following surgical clipping of an aneurysm of the anterior circulation.

Case Reports

Case 1

A 42-year-old woman was brought to our institute with headache and confusion. On arrival, her neurologic status was Hunt and Hess grade III (7). Computed tomography (CT) revealed extensive subarachnoid blood within the basal cistern and both sylvian fissures. Angiography showed an 8-mm aneurysm of the anterior communicating artery (Fig 1A). Surgical clipping was performed on the second day following hemorrhage. After surgery, the patient was able to move all extremities in accordance with commands and her eyes were open. She was treated by volume expansion, hemodilution, and hypertension for vasospasm. Six days after the subarachnoid hemorrhage, the patient's condition suddenly deteriorated: she became much less responsive, with her consciousness declining into semicoma. CT scans showed mild edema.

The right femoral artery was catheterized by placement of a 7F sheath (Terumo Corp, Tokyo, Japan). Angiography showed mild diffuse vasospasm of both the carotid portions, A1 and M1, with more severe diffuse vasospasm of the distal segment of the anterior and middle cerebral arteries, bilaterally (Fig 1B). By use of a roadmap, a coaxial catheter system using a 3F to 2.5F microsoft stream catheter (Target Therapeutics, Fremont, Calif) was advanced into the C2 portion of the intracranial carotid artery. From this position, 80 mg of papaverine was repeatedly infused into the left carotid territory over 15 minutes; two injections, for a total dose of 160 mg, were given. There were no remarkable changes in the patient's symptoms or in the angiographic findings within 30 minutes (Fig 1C). Consequently, 100 mg of amrinone was infused over 5 minutes from the same portion of the carotid artery. Angiography revealed a slight response with some dilatation of the A1 and M1 segments of the carotid artery. An additional 100 mg of amrinone was infused. Angiograms obtained after this infusion showed a mild reversal of the vasospasm in the left distal segments of the anterior and middle cerebral arteries (Fig 1D). Then, 200 mg of amrinone was infused into the right intracranial carotid artery.

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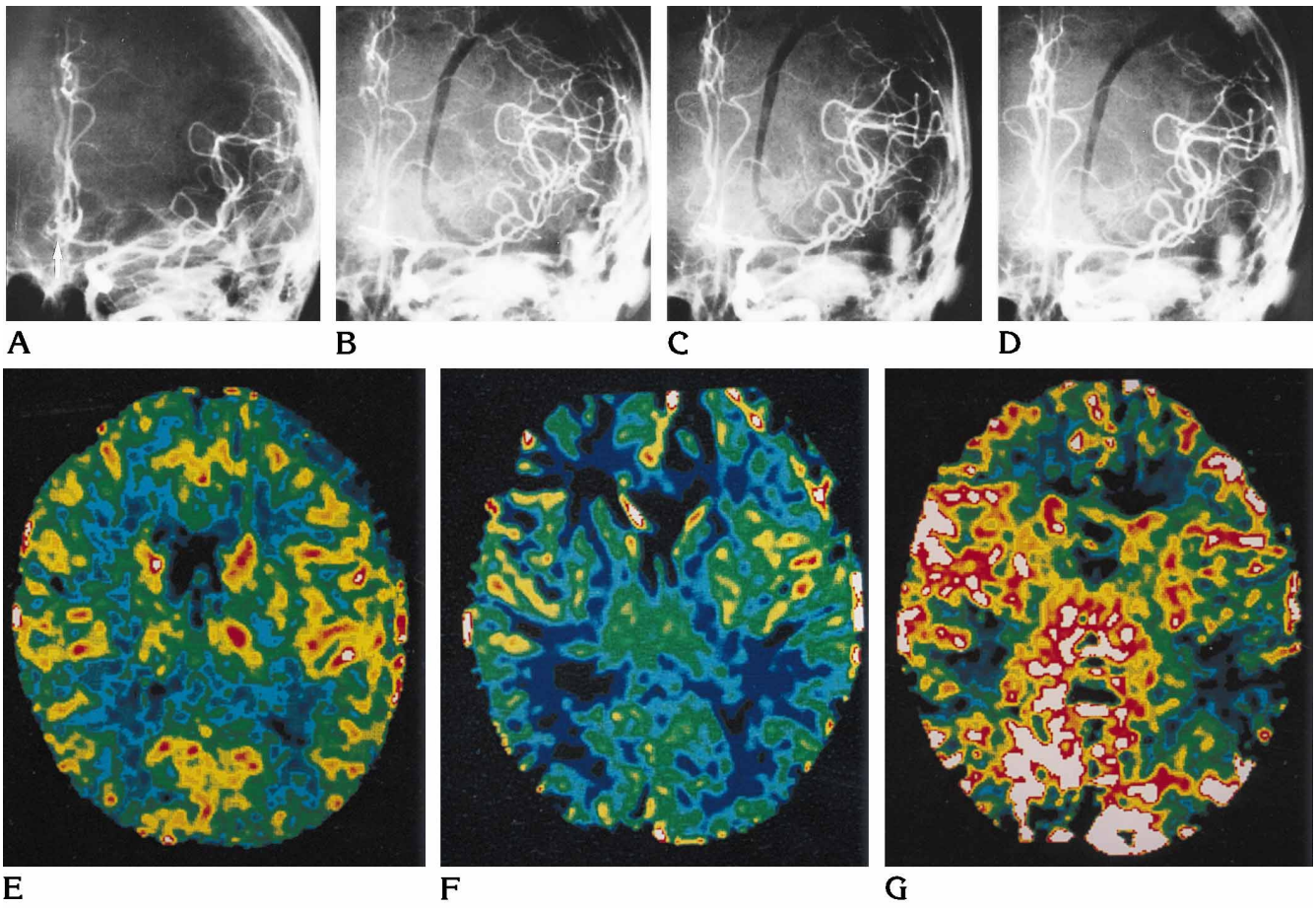

Fig 1. A 42-year-old woman with subarachnoid hemorrhage from an aneurysm of the anterior communicating artery.

A, Anteroposterior left internal carotid artery angiogram shows an aneurysm of the anterior communicating artery at the junction of the two A1 segments (*arrow*).

B, Anteroposterior left internal carotid artery angiogram obtained 6 days after subarachnoid hemorrhage shows diffuse vasospasm.

C and *D*, Anteroposterior left internal carotid artery angiograms obtained after the papaverine injection (*C*) and after the amrinone injection (*D*). The angiographic vasospasm is slightly reversed after the injection of amrinone as compared with that after the papaverine infusion. On the other hand, the symptomatic vasospasm was significantly reversed after the amrinone infusion.

E–G, CBF measurements by cold xenon CT. CBF mapping at the level of the thalamus 3 days after subarachnoid hemorrhage (*E*) and before (*F*) and after (*G*) intraarterial injection of papaverine followed by intraarterial injection of amrinone. The value of the CBF in both hemispheres 3 days after subarachnoid hemorrhage was 32.4 mL/100 g per minute. A marked increase in CBF was noted after the intraarterial injection of amrinone. The values of the CBF in both hemispheres increased from 25.4 mL/100 g per minute to 44 mL/100 g per minute.

After this amrinone infusion, transient hypotension developed, which was controlled by dopamine infusion. (Use of amrinone in patients with cerebral vasospasm had been approved by the committee on human rights in research at our hospital.)

Serial cerebral blood flow (CBF) measurements performed with the xenon-enhanced CT method were obtained using a 3-minute wash-in and 5-minute wash-out protocol with 30% xenon gas 3 days after the subarachnoid hemorrhage, as well as before and after intraarterial infusion (Fig 1E–G). A marked increase in CBF was noted after the intraarterial injections of amrinone.

The patient followed commands immediately after the arterial infusion procedure was complete, and she was almost fully alert without focal deficit 8 hours later. This improvement persisted throughout her hospital stay. One year after the subarachnoid hemorrhage, the patient was intellectually and physiologically normal.

Case 2

A 45-year-old man was brought to our institute with severe headache. On arrival, his neurologic status was Hunt and Hess grade I. CT revealed no subarachnoid blood or other abnormal findings. However, subarachnoid hemorrhage was confirmed by bloody cerebrospinal fluid taken from lumbar puncture. Angiography showed no aneurysm and no vasospasm. Six days after the subarachnoid hemorrhage, the patient suddenly reported severe headache, which was followed by deterioration of his level of con-

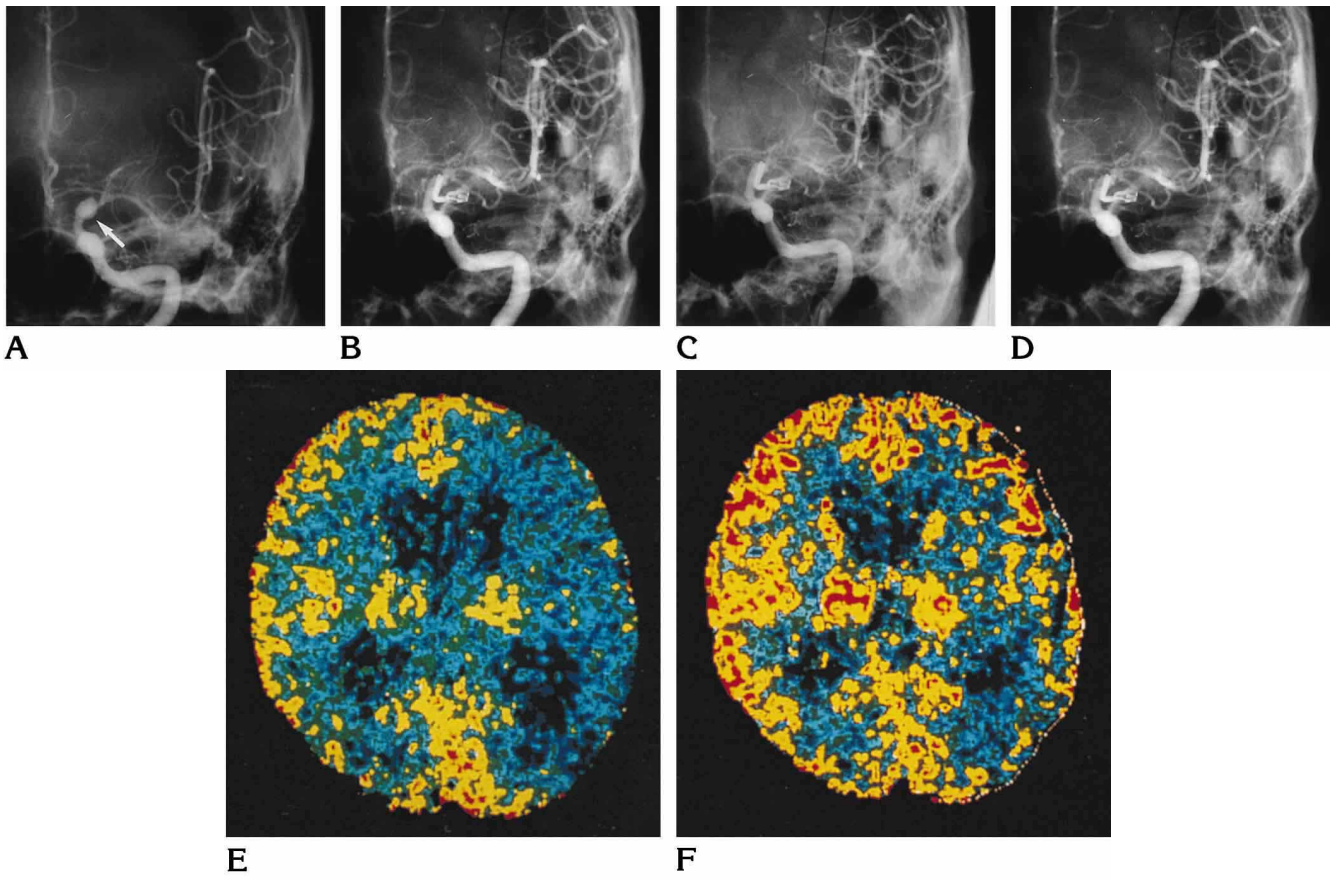

Fig 2. A 45-year-old man with subarachnoid hemorrhage from an aneurysm of the internal carotid artery.

A, Anteroposterior left internal carotid artery angiogram shows a saccular aneurysm of the internal carotid artery (*arrow*) and diffuse vasospasm of the anterior and middle cerebral arteries on the day of the second hemorrhage.

B and *C*, Anteroposterior left internal carotid artery angiograms obtained before (*B*) and after (*C*) papaverine injection.

D, Anteroposterior left internal carotid artery angiogram obtained after amrinone injection. The angiographic vasospasm is not reversed after the injection of papaverine. A mild but positive reversal of the angiographic vasospasm is achieved after the injection of amrinone following the papaverine injection as compared with that after the papaverine infusion.

E and *F*, CBF measurements by cold xenon CT. CBF mapping at the level of the thalamus 6 days after the second hemorrhage (*E*) and after intraarterial injection of papaverine followed by intraarterial injection of amrinone (*F*). The values of the CBF in the left and right hemispheres just after the second hemorrhage were 22.6 mL/100 g per minute and 30.8 mL/100 g per minute, respectively. A marked increase in CBF was noted after the intraarterial injection of amrinone. The values of the CBF in the left and right hemispheres after the amrinone injection were 31.3 mL/100 g per minute and 39.8 mL/100 g per minute, respectively.

sciousness. A CT scan revealed extensive subarachnoid blood within the basal cisterns, perimesencephalic cistern, and right sylvian fissures, and marked ventricular dilatation. Angiography showed a 12-mm aneurysm of the internal carotid artery and severe diffuse vasospasm of the left carotid portions, A1 and M1, with mild diffuse vasospasm of the distal segment of the anterior and middle cerebral arteries (Fig 2A). A preoperative CBF study disclosed a low-flow area at the territory of the middle cerebral artery, which corresponded to the angiographic vasospasm (Fig 2E). Surgical clipping and ventricular drainage were performed on the day of the second subarachnoid hemorrhage. After surgery, intraarterial injections of papaverine and amrinone were administered by means of the procedure described in case 1: 80 mg of papaverine was repeatedly infused over 15 minutes from the intracranial C2 portion of the carotid artery, for a total dose of 240 mg. No remarkable change was noted in the patient's symptoms or in the angiographic findings within 30 minutes (Fig 2B and C). As the next step, 100 mg of amrinone was infused over 5 minutes from the left intracranial portion of the carotid artery. Angiography revealed a slight response with some dilatation of the A1 and M1 segments of the carotid artery. An additional 100 mg of amrinone was infused. Angiograms obtained after this infusion showed a mild but obvious reversal of the vasospasm in the left carotid A1 and M1 segments as well as the distal portion of the anterior and middle cerebral arteries (Fig 2D). An additional 200 mg of amrinone was infused into the left carotid artery, after which no hypotension was apparent; however, the patient was continuously infused with intravenous dopamine to maintain a systolic blood pressure

above 160 mm Hg. A marked increase in CBF was noted after the intraarterial injections of amrinone (Fig 2F).

The patient's consciousness level improved just after completion of the procedure, and there were no focal deficits 24 hours later. This improvement persisted throughout his hospital stay, and 2 months after the subarachnoid hemorrhage, he returned to his job.

Discussion

Papaverine has been used to treat cerebral vasospasm after subarachnoid hemorrhage in patients with aneurysmal rupture (1, 2). The vasodilatory effects of this drug on spastic vessels have been investigated experimentally by several authors (7–9). Papaverine is known to be one of the common nonselective inhibitors of the phosphodiesterase isozyme families (10). A role for cyclic nucleotides has been postulated in the contraction-relaxation cycles of vascular smooth muscle in relation to the concentration of free calcium ion in the vascular smooth muscle cells (11). Different molecular forms of phosphodiesterases (PDEs) have been isolated from cardiac muscle and vascular smooth muscle. At least five different isozyme families of cyclic nucleotides PDEs are presently recognized (10). A low K_m, low V_{max} form of PDE I has been found in all cardiac and vascular smooth muscles. Such PDE I activity was stimulated by calmodulin. Amrinone and milrinone have been shown to exhibit selective inhibition of the low K_m, low V_{max} cyclic adenosine monophosphate (cAMP) phosphodiesterase–specific PDE (PDE III) isolated from cardiac muscle (12), and the activity of PDE III was not stimulated by calmodulin. The low K_m, low V_{max} cAMP-specific PDE III of vascular smooth muscle is pharmacologically similar to the peak PDE III in cardiac muscle (13). It has been reported that increases in intracellular cAMP content occurring as a consequence of PDE inhibition by PDE III inhibitors can cause relaxation of vascular smooth muscle (13, 14).

Amrinone behaves as a positive inotropic agent with a vasodilator activity based on inhibition of PDE. Amrinone is a pale yellow crystalline compound with a molecular weight of 187.2 and an empirical formula of C10H9N30. Sodium metabisulfite is added as a preservative, and the pH of amrinone is adjusted to between 3.2 and 4.0 with lactic acid or sodium hydroxide. Amrinone is indicated for use in the management of congestive heart failure. Following an intravenous bolus injection (1 to 2 minutes) of amrinone of 0.75 mg/kg to 3 mg/kg in patients with congestive heart failure, cardiac output undergoes a dose-related increase, and the pulmonary capillary wedge pressure and total peripheral resistance exhibit dose-related decreases. A total dose of amrinone of 3 mg/kg for intraarterial injection was therefore considered to be the maximum dose for the patients reported here.

We are unable to explain clearly the incomplete reversal effect of intraarterial amrinone infusion in our two patients with postoperative vasospasm refractory to injection of papaverine. Although the angiographic vasospasm failed to show a marked improvement, the symptomatic vasospasm was dramatically improved and a marked increase in CBF was noted after the infusion of amrinone following papaverine infusion in both cases.

The degree of selectivity of PDE and the effects of several PDE inhibitors have been found to be dependent on the tissues examined in an experimental study (15). It is inferred that amrinone might have the capacity to dilate vessels showing cerebral vasospasm caused by derangement of vascular muscle contraction and relaxation. Alternatively, smaller vessels corresponding to the microcirculation of the brain as compared with the large vessels depicted by angiography might be dilated after injection of amrinone, resulting in the improvement noted on CBF mapping. In addition, the intravenous infusion of dopamine might influence the cerebral circulation through an increase in cardiac output combined with the positive inotropic action of amrinone.

Our cases represent the first trial of intraarterial injection of amrinone for reducing cerebral vasospasm. Neither patient had unfavorable side effects after the injection, and clinical symptoms and CBF were improved by the intraarterial amrinone administered after intraarterial injection of papaverine, although angiograms obtained after the amrinone infusion showed only a mild reversal of the vasospasm. Further studies are needed to establish a rationale and mechanism for the use of inhibitors of the PDE families in cerebral vasospasm. The safety and effectiveness of amrinone therapy for patients with cerebral vasospasm should be examined in detail with more subjects.

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