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Intracranial pressure changes induced during papaverine infusion for treatment of vasospasm

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The authors reviewed the cases of 21 patients who received intraarterial infusions of papaverine to determine the drug's effects on intracranial pressure (ICP), mean arterial blood pressure, pulse rate, and cerebral perfusion pressure (CPP). The study focused on patients with aneurysmal subarachnoid hemorrhage who developed clinical signs and symptoms of vasospasm, which was documented by cerebral angiography. In 18 patients, an average dose of 300 mg papaverine was administered over 20 to 35 minutes using a No. 5 French catheter inserted into the high cervical internal carotid artery or vertebral artery. Two other patients received superselective infusions via a microcatheter placed in the anterior cerebral artery.

Sixteen patients (76%) experienced good angiographic results, and 11 (52%) obtained objective clinical improvement within 48 hours. Significant elevations in ICP, blood pressure, and pulse rate were noted during papaverine infusion. In contrast, no statistically significant sustained change in CPP was observed, although it tended to decrease during papaverine infusion. In one elderly patient, infusion of the common carotid artery resulted in profound bradycardia and hypotension with a subsequent significant increase in ICP and a marked decrease in CPP. The increase in ICP in these patients correlates well with changes seen in animal models and is probably related to increased cerebral blood flow.

A careful, titrated infusion of papaverine, with constant reference to the patient's ICP, blood pressure, and pulse rate, minimizes the transient increase in ICP while maintaining adequate blood pressure and CPP. Failure to monitor these parameters during the infusion, with appropriate modification of the rate of titration, could potentially produce an uncontrolled change in ICP or CPP.

KEY WORDS • cerebral vasospasm • papaverine • angioplasty • subarachnoid hemorrhage

CEREBRAL vasospasm induced by aneurysmal subarachnoid hemorrhage (SAH) is still a leading cause of morbidity and mortality, despite advances in treatment.[1,6,9,14] Neurological deficit can develop secondary to delayed ischemia in up to 30% of patients.[9,14] Hypertensive, hypervolemic hemodilution,[1] calcium channel blocking agents,[21] and early surgery with clot removal[8] have been reported to decrease the severity and incidence of vasospasm. More recently, balloon angioplasty has been increasingly used with effective results in some patients.[3,10,20] Angioplasty is most useful in proximal vessels, but has limited ability to reach distal vessels and the A_1 segment of the anterior cerebral artery (ACA).[12]

Intraarterial administration of papaverine, a potent vasodilator, is advocated for relief of distal spasm[2,12,13] and for use as an adjunct to angioplasty.[16,18] Animal models have been used to evaluate the changes in intracranial pressure (ICP) induced by papaverine infusion.[4,15,17,19,22,23] The potential changes in ICP, blood pressure (BP), pulse, and cerebral perfusion pressure (CPP) induced by intraarterial papaverine infusion in humans, to our knowledge, has not been previously reported. The present report details such changes demonstrated during infusion of papaverine in patients with symptomatic vasospasm induced by SAH.

Clinical Material and Methods

Patient Population

From July 1992 through November 1993, 21 patients (16 women and five men) aged 31 to 74 years were referred to the neurointerventional radiology service of Harborview Medical Center for treatment of aneurysmal SAH–induced, symptomatic cerebral vasospasm. The majority of the patients were treated entirely at this medical center, although four were referred for treatment of symptomatic vasospasm after aneurysm clipping had been performed elsewhere. Patients admitted to the study fulfilled the following criteria: 1) clinical deterioration; 2) rising transcranial Doppler velocities; 3) regions of decreased attenuation, suggesting ischemia on computerized tomography (CT); 4) regions of hypoperfusion that were detected with a single-photon emission computerized tomogra-

phy brain study; and 5) angiographic evidence of vasospasm. The hospital records of all of these patients were reviewed and alterations in ICP, mean arterial BP (MABP), and pulse rate during the treatment procedure were examined. Intracranial pressure was measured using subarachnoid pressure bolts. Blood pressure and pulse rates were constantly recorded with intraarterial catheters. Doses of the treatment drug, papaverine, and rates of infusion were also noted, as were any complications occurring during the procedure. The CPP was calculated (ICP − MABP) and the results were subjected to a nonparametric statistical analysis using the Wilcoxon signed-rank test.

Treatment Procedure

After completion of an angiogram, a No. 5 French vertebral catheter was inserted though a No. 7 French sheath, and the catheter tip was placed into the high cerebral internal carotid artery (ICA) or vertebral artery (VA) on the affected side. All patients, except one (Case 7), were sedated and intubated for the procedure.

In the first two cases, a microcatheter was placed into the A_1 segment through a No. 7 French guiding catheter. Subsequently, the routine methodology became to infuse papaverine via the No. 5 French catheter in the distal cervical ICA or VA.

Three hundred milligrams of papaverine hydrochloride was diluted in normal saline for a total volume of 22 to 24 ml. This was gently infused by hand, using tiny puffed aliquots with constant reference to pulse, MABP, and ICP recordings. The rate of infusion was titrated according to these parameters, but usually extended to 20 to 35 minutes. Ideally, ICP was kept below 20 mm Hg and infusions were slowed or stopped if ICP levels rose. If the patient tolerated 300 mg papaverine, a repeat angiogram would then be performed and additional papaverine administered to a maximum dose of 500 mg/vessel if no significant vessel caliber change was demonstrated. Angioplasty was performed, if required, in patients with refractory proximal vessel spasm. In four patients with high-grade ACA spasm and no middle cerebral artery (MCA) spasm, a temporary balloon occlusion of the M_1 segment of the MCA was performed (using an angioplasty balloon) to facilitate the papaverine flow to the ACA. In a single patient (Case 15), papaverine was infused in the common carotid artery (CCA) because this patient had extensive atheroma with tortuous vessels and bifurcation disease. Superselective catheterization with a microcatheter was not performed. As a result, the distal CCA and carotid bulb were perfused with papaverine.

Patient characteristics are displayed in Table 1.

Results

A total of 42 vessels (ICA, CCA, ACA, and VA) were perfused with papaverine in 21 patients. Four of the patients were treated twice and one patient three times. Twelve patients received subsequent angioplasty to 34 vessel segments (ICA, M_1, M_2, VA, basilar artery (BA), and P_1).

Eleven patients (52%) had objective clinical improvement within 48 hours of therapy. This was measured by a two-point increase in the Glasgow Coma Scale score. Sixteen patients (76%) had a good angiographic response (40%–100% luminal diameter increase) following initial therapy. The detailed results of treatment and accompanying changes in ICP, CPP, BP, and pulse rate are detailed in Table 1 and Fig. 1.

Three patients died during endoluminal therapy. The first patient (Case 1) died after balloon angioplasty-induced rupture of a P_1 segment. A second patient (Case 17) had a 95% refractory narrowing of the ICA, despite papaverine infusion and angioplasty. Computerized tomography evidence of a developing large left hemisphere infarct prompted urokinase infusion 3 days later to relieve the occlusion. This resulted in a large epidural hematoma and subsequent death. The third patient (Case 7) became symptomatic with a fatal basal ganglia hemorrhage during angioplasty of the right M_1 segment immediately after papaverine infusion. The patient's ICP was labile throughout both endovascular procedures. Autopsy did not reveal an M_1 rupture. The cause of the hemorrhage is speculative, but the change in ICP, with a peak of 35 mm Hg, may well have contributed to this event.

The observable changes in ICP ($p < 0.0001$), pulse ($p = 0.040$), and CPP ($p = 0.045$) were all statistically significant. The change in MABP ($p = 0.066$) did not reach statistical significance.

In all but one instance (Case 15), the CPP remained above 58 mm Hg. This patient had profound bradycardia on both occasions when papaverine was infused into the CCA. On the second occasion, first-degree heart block ensued with accompanying hypotension and markedly decreased CPP. The infusion of the CCA and carotid bulb differs significantly from standard practice. If this patient is excluded from analysis, application of the same Wilcoxon signed-rank test results in statistically significant observable changes in mean ICP ($p < 0.0001$), mean pulse ($p = 0.0039$), and MABP ($p = 0.011$). No statistically significant change in mean CPP ($p = 0.114$) was observed.

Discussion

We reviewed the cases of 21 patients undergoing papaverine infusion for the treatment of SAH-induced vasospasm and have noted a significant increase in ICP, MABP, and pulse rate during treatment. Intraarterial papaverine is being used increasingly in the instances of vasospasm that is induced by SAH.[2,12,13,16,18] Papaverine is an alkaloid of the opium group, which induces vasodilation of cerebral and coronary arteries by its direct action on inhibiting smooth-muscle contraction.[7,12]

Animal models have been used to evaluate changes in ICP and BP induced by papaverine infusion. The resultant significant increase in ICP is thought to be attributable to its vasodilatory action,[17,19] which similar to that of histamine and nitroglycerine[6,22,23] results in an increase in cerebral blood flow (CBF). An additional animal study demonstrated transient hypotension in 45% of cases after papaverine infusion into the VA.[15] This change was proportional to dose, and cardiac arrhythmia and subsequent death were seen with prolonged hypotension.

Groups using the drug for treatment of vasospasm in humans have reported good results. However, changes in

TABLE 1

*Clinical summary of 21 patients treated with intraarterial papaverine infusion**

Case No.	Age (yrs), Sex	PAV (mg)/ Infusion Time (min)	Vascular Territory Treated	Angiographic Improvement†	Location Angioplasty Applied	Clinical Improvement	Complications
1	57, F	300/25	lt ACA‡	moderate	lt ICA; M_1; M_2; BA; lt P_1	no	rupture of lt P_1 & death
2	39, M	300/30	lt ACA‡	marked	rt ICA; M_1	no	
		300/30	rt ACA‡				
		300/40	lt ICA	moderate		no	
		300/40	rt ICA				
3	42, F	260/25	rt VA; BA	moderate		yes	
4	54, F	240/25	lt VA; BA	moderate	BA	yes	
		300/25	rt ICA				
5	49, F	300/20	lt ICA	moderate	rt ICA; M_1; lt ICA; M_1	yes	
6	35, F	420/40	rt ICA	marked		yes	
7	38, F	360/50	rt ICA	moderate	rt ICA; M_1	no	rt basal ganglia hemorrhage resulting in death 3 days later
8	54, M	120/25	rt ICA	marked	rt ICA; M_1	yes	
		240/25	rt ICA; ACA§				
		300/25	lt ICA				
9	64, F	300/15	rt ICA	moderate		yes	
10	52, F	120/25	lt ICA	marked		yes	
11	52, F	360/25	lt ICA	moderate	lt ICA; M_1;	no	died 3 days later
		300/30	lt ICA; ACA§		rt ICA; M_1;		
		240/15	lt VA; BA		BA		
		240/30	rt ICA; ACA§				
12	31, M	300/25	rt ICA	mild	rt ICA; M_1	yes	
13	74, F	300/30	lt ICA	moderate		no	
		300/25	rt ICA				
		300/20	rt ICA	marked		yes	
		300/20	lt ICA				
14	63, M	300/20	lt ICA	moderate		no	
		300/25	rt ICA	moderate		no	
		300/30	lt ICA				
		300/25	rt ICA	mild		no	
		300/25	lt ICA				
15	63, F	450/50	rt CCA	moderate		no	bradycardia
		300/20	lt CCA				
		450/75	rt CCA	none		no	first degree heart block
		300/40	lt CCA				
16	38, F	360/30	rt ICA	none	lt ICA; M_1;	no	severe spasm; died 1 day later
		360/30	lt ICA		rt ICA; M_1; BA		
17	45, F	380/50	lt ICA	none	lt ICA	no	95% ICA stenosis; died of epidural hematoma related to urokinase
18	53, F	480/50	lt ICA	mild	lt M_1	no	
19	55, F	300/30	rt ICA	moderate		no	
20	67, M	300/15	rt ICA	marked	rt ICA; M_1;	yes	
		300/12	lt ICA		lt ICA; M_1		
		300/40	rt ICA	moderate		no	
21	50, F	300/25	rt ICA	mild		yes	

* Abbreviations: PAV = papaverine; ACA = anterior carotid artery; ICA = internal carotid artery; M_1, M_2 = segments of middle cerebral artery; BA = basilar artery; P_1 = P_1 segment; VA = vertebral artery; CCA = common carotid artery.

† Angiographic improvement in luminal diameter following administration of papaverine: mild = 10%–30%; moderate = 40%–60%; marked = 70%–100%.

‡ Infusion of PAV into ACA via microcatheter.

§ Infusion of PAV into ICA with angioplasty balloon occluding M_1 segment.

ICP or CPP secondary to papaverine infusion in humans have not yet been documented in the literature. One group reports pulse rate increases of 10% to 20%,[12] even though superselective injections were administered with microcatheters. Another group[13] has reported no significant change in BP despite 300-mg doses of papaverine per hour infused via the ICA or VA.

Our experience has shown that significant changes in ICP, BP, and pulse rate can occur with superselective injection of papaverine using a microcatheter in the A_1 segment (Cases 1 and 2) as well as with ICA infusion. Infusion via the ICA using a No. 5 French vertebral catheter is quick, less invasive, and easier; it treats two vascular territories at once, as it is common to have vasospasm in the supraclinoid ICA, MCA, and ACA simultaneously. Selective ACA spasm can be managed by superselective infusion using a steerable microcatheter. Alternately, temporary gentle inflation of a vasospasm balloon in the M_1 segment during papaverine infusion via the high cervical ICA can be performed. The dose of papaverine that can

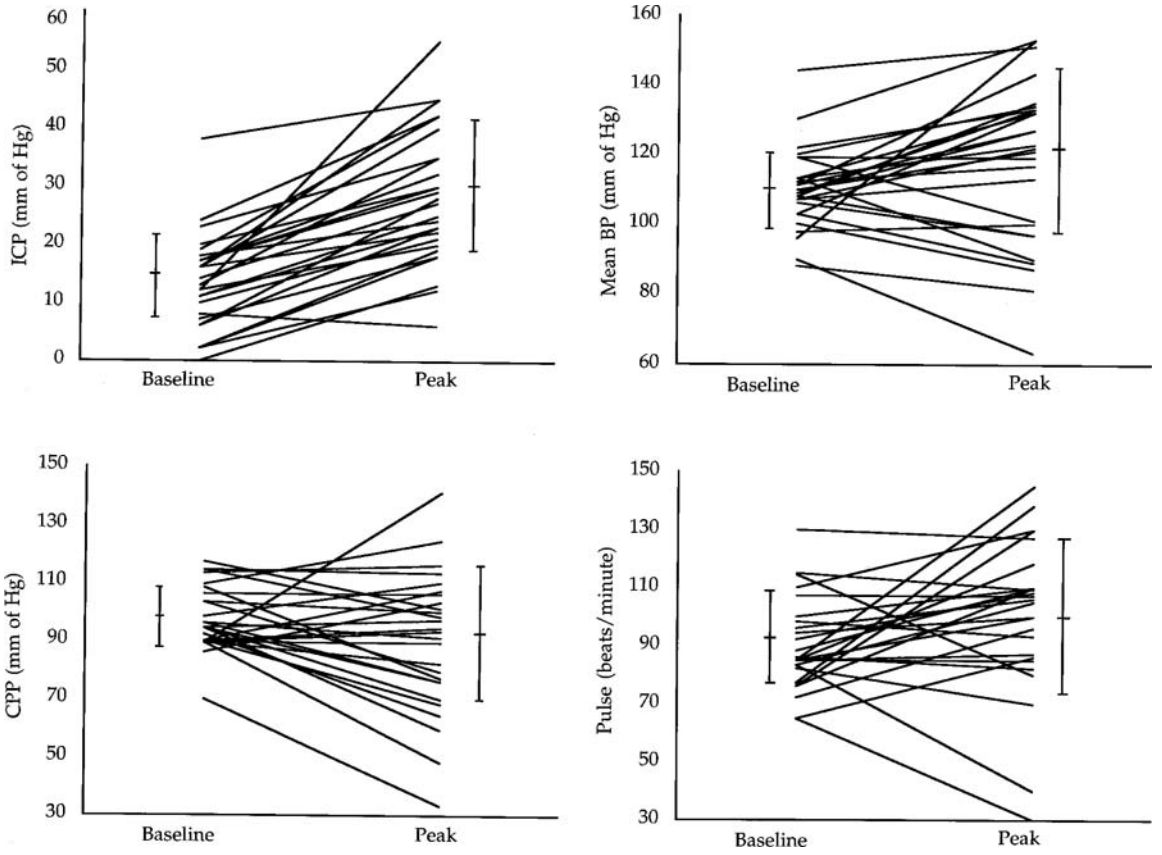

FIG. 1. Graphs depicting the effects of papaverine infusion on intracranial pressure *(upper left)*, mean arterial blood pressure *(upper right)*, cerebral perfusion pressure *(lower left)*, and pulse rate *(lower right)*. The mean value and standard deviation *(vertical bar)* are also plotted in each instance.

safely be used has not been firmly established, but average doses of 300 mg have been reported.[13,18] We found that by constant reference to ICP, BP, and pulse recordings, the dose in each vessel can be titrated without need for a formal dose rate. Using constant hemodynamic monitoring, any significant changes in mean ICP, MABP, and pulse rate can be detected early, enabling the CPP to be safely maintained by adjusting the infusion rate. Normally, CPP is approximately 75 mm Hg and should ideally exceed 55 to 60 mm Hg to maintain an adequate perfusion of the cerebral capillary bed.[11] In all but two patients (Cases 15 and 19), the CPP was maintained above 60 mm Hg during treatment. In only one instance (Case 15) did the CPP fall below 55 mm Hg. It is perhaps significant that this was the only patient who received an infusion of papaverine via the CCA. This infusion resulted in profound bradycardia (30 beats min), followed by hypotension (MABP 63 mm Hg) and a subsequent rise in ICP that resulted in low CPP (33 mm Hg). We would therefore caution against a CCA infusion because it results in direct perfusion of the carotid body, which may have been responsible for the changes that occurred. Although the ICP commonly rose above 20 mm Hg in the cases studied, the increases were transient (1–5 minutes) and sensitive to the rate of infusion, and the concomitant increases in BP were usually sufficient to maintain an adequate CPP. Adequate BP and CPP correlate with a tolerance of transient increased ICP.[4]

In our experience, papaverine is a useful adjuvant to angioplasty, as previously noted.[18] Preinfusion of papaverine has made balloon dilation of the ICA and M_1 segments easier. Papaverine can also be used in the treatment of distal spasm in vessels not accessible to angioplasty. Even small changes in vessel caliber translate into significant alterations in CBF, as cerebral vascular resistance is theoretically proportional to the fourth power of the vessel radius.[4] Seventy-six percent of patients had a 40% to 100% increase in vessel diameter after papaverine infusion, with 52% demonstrating clinical improvement following papaverine administration and angioplasty. We would caution, however, that angioplasty and intraarterial papaverine infusion is not a benign treatment. One patient (Case 7) had a fatal right basal ganglia hemorrhage following intraarterial administration of papaverine and subsequent angioplasty of the right M_1 segment. No rupture of the M_1 segment was seen at autopsy and the exact cause of the hemorrhage is therefore uncertain. Changes in the peak ICP and MABP during infusion of papaverine in this patient were unremarkable when compared to the rest of the patient population, but the ICP was labile before and during the infusion. The peak ICP of 35 mm Hg may have contributed to the precipitation of this hemorrhage.

Patients with symptomatic vasospasm are very ill and may have impaired vascular autoregulatory mechanisms. The changes in ICP and CPP that occur during papaverine

infusion in some patients may reflect, in part, this lack of autoregulation. It is difficult to test safely whether this is the case in symptomatic patients and we did not attempt to do so in this study. However, changes in ICP, BP, CPP, and pulse rate were monitored, and the magnitude and rapidity of these changes during infusion of papaverine were observed to be unpredictable in many cases. Therefore, in practical terms, strict attention to ICP, BP, pulse, and CPP is required in all cases of patients treated with papaverine, either superselectively or via the ICA. The use of papaverine in unprotected ruptured aneurysms requires special caution because regional blood flow increases may theoretically precipitate a further hemorrhage. We have been able to minimize the hemodynamic changes by careful titration of the papaverine infusion. Failure to do so could potentially result in a sudden significant increase in ICP and a concomitant decrease in CPP, resulting in further ischemic compromise of a brain already at risk.

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