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Papaverine-Induced Mydriasis

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Summary: Five cases of ipsilateral pupillary dilatation that developed during local intraarterial infusion of papaverine are reported. All patients were being treated for symptomatic vasospasm secondary to subarachnoid hemorrhage. In each case, the tip of the infusion catheter was positioned in the internal carotid artery in close proximity to the ostium of the ophthalmic artery. Pupillary dilatation in all patients readily resolved after termination of the infusion.

Index terms: Vasospasm; Drugs, reaction; Interventional neuroradiology, complications of; Iatrogenic disease or disorder; Eyes, abnormalities and anomalies

The use of local intraarterial infusion of papaverine hydrochloride for the treatment of cerebral artery vasospasm has been described (1–5). Twenty-three patients (34 vessels infused) with angiographically confirmed vasospasm have been treated at our institution. We have observed ipsilateral pupillary dilatation in all five patients (five of six infusions) in whom the infusion catheter tip was positioned in the internal carotid artery within a few millimeters of the ophthalmic artery ostium. Pupillary dilatation was not observed during any vertebrobasilar infusions or internal carotid artery infusions distal to the ophthalmic artery origin, nor in one case in which the catheter tip was positioned in the cervical internal carotid artery. In this report, we describe papaverine-induced mydriasis, propose a likely mechanism, and discuss its clinical significance.

Case Reports

Case 1

A 47-year-old woman had symptomatic vasospasm 6 days after aneurysm clipping. Transcranial pulsed Doppler examination was consistent with severe left middle cerebral artery vasospasm; this was confirmed with angiography. A Tracker 18 infusion catheter (Target Therapeutics, Fremont, Calif) was positioned with the tip in the ophthalmic portion of the left internal carotid artery; a continuous infusion of papaverine at the rate of 5 mg/min was begun. After the patient had received approximately 170 mg of papaverine, acute dilatation of only the left pupil was noted. The infusion was terminated and the pupillary dilatation resolved within 15 minutes. No other neurologic changes were observed during the infusion. We noted in retrospect that the catheter tip had been within 1 to 2 mm of the ophthalmic artery ostium during the infusion.

Case 2

A 59-year-old man had symptomatic vasospasm of the proximal left middle cerebral artery and supraclinoid internal carotid artery 10 days after subarachnoid hemorrhage secondary to a dissecting aneurysm of the vertebral artery and 5 days after permanent balloon occlusion of the right vertebral artery. A Balt Magic 1.5-F infusion catheter (Target Therapeutics) was advanced coaxially through a guiding catheter into the intracranial internal carotid artery. The tip was advanced as distally as possible, in this case 6 to 8 mm proximal to the ostium of the ophthalmic artery, and a continuous infusion of papaverine (300 mg in 100 mL of normal saline) at a rate of 6 mg/min was begun. After the patient had received approximately 60 mg of papaverine, acute dilatation of the ipsilateral pupil with nonreactivity to light was noted. The contralateral pupil remained unchanged in size and demonstrated both direct and consensual reaction to light. We observed no other neurologic changes, and so continued the infusion. Twenty minutes later, when the patient had received approximately 225 mg of papaverine, the dilatation of the pupil had lessened. Forty-five minutes after the beginning of the infusion, at which time the patient had received the full dose of 300 mg of papaverine, the pupil had returned to baseline. During the entire 45 minutes of infusion, the patient's vital signs and neurologic status remained stable.

Case 3

Vasospasm developed in a 43-year-old woman 1 day after her admission for subarachnoid hemorrhage. Diagnostic angiography had demonstrated a large, irregular aneurysm of the ophthalmic segment of the internal carotid artery. Repeat angiography demonstrated severe vasospasm of the right supraclinoid internal carotid artery, A-1 and M-1 segments, and prolonged cerebral circulation time; there was mild vasospasm of the left supraclinoid internal carotid artery, A-1 and M-1 segments. The right internal carotid artery aneurysm was embolized with two 5 × 15-

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mm Gugliemi detachable platinum coils (Target Therapeutics). The Tracker 10 coil microcatheter could not be positioned satisfactorily distal to the embolized aneurysm; continuous infusion of papaverine at a rate of 6 mg/min was begun with the catheter tip positioned 6 to 8 mm proximal to the right ophthalmic artery ostium. Before infusion, both pupils measured 4 mm and demonstrated brisk reaction to light, both direct and consensual. Thirteen minutes after beginning the infusion, the right pupil measured 6 to 7 mm and was fixed; the left pupil was unchanged in size and continued to react briskly. No other change in the patient's neurologic status was observed. Twenty-six minutes after starting the papaverine infusion, the right pupil measured 5 mm and remained unreactive to light; the left pupil was unchanged. Fifteen minutes after concluding the infusion of 300 mg of papaverine, the right pupil had returned to baseline size and was sluggishly reactive to light. Sixty minutes after concluding the papaverine infusion, both pupils measured 3 to 4 mm in diameter and were briskly responsive.

Case 4

Vasospasm of both anterior cerebral arteries developed in a 67-year-old woman 8 days after clipping of an anterior communicating artery aneurysm. A Tracker 18 infusion catheter could not be satisfactorily positioned in the left anterior cerebral artery or supraclinoid internal carotid artery. The infusion catheter tip was positioned in the cavernous portion of the left internal carotid artery, approximately 15 mm proximal to the ophthalmic artery ostium, and 300 mg of papaverine in 100 mL of normal saline was infused continuously for 40 minutes. Pupillary dilatation was not observed. Superselective infusion of the right anterior cerebral artery was then attempted but could not be obtained. The infusion catheter tip was positioned in the right internal carotid artery, approximately 8 to 10 mm proximal to the ophthalmic artery ostium, and 300 mg of papaverine was infused for 40 minutes. Twenty minutes after beginning the infusion, we observed dilatation and lack of response to light of the right pupil. By the end of the infusion, dilatation of the right pupil was less pronounced; 15 minutes after ending the infusion, the dilatation had resolved.

Case 5

Vasospasm of both anterior cerebral arteries developed in a 64-year-old woman five days after clipping of the right middle cerebral artery and anterior communicating artery aneurysms. Three hundred milligrams of papaverine was infused through a Tracker 10 infusion catheter superselectively into the left anterior cerebral artery continuously for 45 minutes. Pupillary dilatation was not observed. The right anterior cerebral artery could not be selectively catheterized; the infusion catheter tip was positioned in the right internal carotid artery, 4 to 5 mm from the ophthalmic artery origin. Three hundered milligrams of papaverine in 100 mL of normal saline was continuously infused into the right internal carotid artery for 45 minutes. Within 15 minutes, dilatation of the right pupil was noted; no other neurologic deficits were evident, and vital signs remained stable. In order to exclude parasympathetic denervation secondary to third cranial nerve compression or anoxia, we administered 0.5% pilocarpine hydrochloride topically to the right eye; no constriction of the pupil was observed. By the end of the papaverine infusion, dilatation of the right pupil had lessened and had resolved 15 minutes after completion of the infusion.

Discussion

Papaverine hydrochloride belongs to the benzylisoquinoline group of alkaloids. The most characteristic effect of papaverine is the relaxation of the tonus of all smooth muscle, especially when it has been spasmodically contracted (package insert; papaverine hydrochloride injection, USP; Eli Lilly, Indianapolis, Ind). This action on the smooth musculature of cerebral (and other) arteries, especially when such vessels are in spasm, provides the basis for the clinical use of papaverine in cerebral artery vasospasm (6).

The relaxation effect of papaverine has been noted in the vascular system and bronchial musculature and in the gastrointestinal, biliary, and urinary tracts. The effects of papaverine on the ocular circulation in animals has been studied; increased ocular blood flow in pigs and monkeys (7) and increased vitreous PO_2 in cats (8) have been demonstrated. We have, however, been unable to document any literature on the effects of papaverine on the anterior segment, particularly the functioning of the iris, in animals or humans.

We hypothesize that papaverine acts directly on the musculature of the iris to produce the dilatation we observed. This is the most likely explanation for the following reasons. First, as noted above, papaverine has produced relaxation of the tonus of all smooth muscle that has been studied to date. It is known from the study and use of ganglionic blocking drugs that the net effect of paralysis of both the dilator and sphincter muscles is incomplete mydriasis (9). It is even possible that there is a selective effect of papaverine on the sphincter as opposed to the dilator muscle, given that the sphincter is composed of true smooth muscle cells, whereas the dilator cells retain a primitive myoepithelial structure (10). If this were the case, we would expect that a directly acting sympathetic stimulator (epinephrine) might further dilate the pupil (11). Second, that dilatation of the pupil was seen only in patients in whom the infusion catheter tip was in close proximity to the ophthalmic artery argues

for a local, as opposed to a systemic, effect. Third, concurrent application of pilocarpine in one patient during the dilatation episode did not produce constriction. If papaverine induces dilatation of the pupil by acting directly on the musculature of the iris, then application of pilocarpine, which would normally cause pupillary constriction even in the setting of ganglionic blockade, should have no effect (11, 12).

All but the first two patients of our series (and all five patients who experienced mydriasis) received papaverine preserved with 0.5% chlorobutanol; papaverine without preservative is not commercially available. In larger doses, chlorobutanol is pharmacologically active and has been used as an oral hypnotic agent in humans in a dose range of 300 to 1200 mg (13); it is structurally similar to trichloroethanol, the active metabolite of chloral hydrate (14). Chlorobutanol has been reported by some investigators to be vasoactive, but others have noted an absence of vasoactivity (15). Although we cannot entirely exclude an effect of chlorobutanol, it is not likely the cause of mydriasis in our patients. Both the concentration and the total amount of chlorobutanol contained in the papaverine solution were very small, and the patients would have received only a fraction of that amount 15 to 20 minutes into the infusion at the time of the onset of pupillary dilatation. Chlorobutanol has been widely used as a preservative in artificial tear solutions and other topical ophthalmic preparations (16) without any reports of pupillary effects.

As noted above in case 4, ipsilateral pupillary dilatation was observed on infusion of papaverine at 8 mm proximal to the left ophthalmic artery origin, but not with infusion 15 mm proximal to the right ophthalmic artery origin. A possible explanation is that with our method of infusion, the critical distance from the catheter tip to the ophthalmic artery ostium for intraarterial delivery of a dose of papaverine sufficient to produce mydriasis is a matter of millimeters; pupillary dilatation was observed only during each infusion in which the catheter tip was less than 10 mm proximal to the ophthalmic artery ostium.

The dilated pupil during a neurointerventional procedure raises the suspicion of the acute onset of cranial nerve III dysfunction. In the responsive patient, this can be excluded based on the lack of involvement of the extraocular muscles (normal ductions and versions and absence of adducting delay) and a normal lid position. In the unresponsive patient, vestibular-induced motility should remain conjugant, showing no weakness in adduction (11). Pupillary drug testing with pilocarpine would be expected to show rapid constriction in the case of cranial nerve III dysfunction (12). Nonetheless, even in the absence of these signs, the unwary therapist could falsely attribute papaverine-induced pupillary dilatation to a serious neurologic event and unnecessarily terminate treatment, as we did initially.

The transient nature of the effect, even when the infusion is continued, remains to be explained. We hope that additional pupillary pharmacologic testing can provide a more detailed explanation. In the interim, neuroradiologists should be aware of this phenomenon.

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