Transient bilateral brainstem dysfunction caused by topical administration of papaverine

Report of 2 cases

Colleen M. Moran, M.D.,1 Michael E. Mahla, M.D.,1 Brett Reichwage, M.D.,2 Stephen Lewis, M.D.,2 Keith Peters, M.D.,3 and Christoph N. Seubert, M.D.1

Departments of 1Anesthesiology, 2Neurosurgery, and 3Radiology, University of Florida, Gainesville, Florida

Papaverine has been associated with transient cranial nerve dysfunction after topical application during craniotomy. The authors report similar dysfunction after the use of papaverine affected brainstem structures. Two patients undergoing craniotomy for clipping of an aneurysm experienced bilateral depression of cortical somatosensory evoked potentials to both median and tibial nerve stimulation after administration of papaverine. Arterial blood gas analysis, hemodynamic parameters, and anesthetic levels remained constant throughout these somatosensory evoked potential changes. In addition, intraoperative angiography and immediate postoperative CT imaging showed intact blood flow with complete exclusion of the aneurysm. Both patients recovered within 1–2 hours and had normal neurological examination findings after extubation. Topical papaverine use may be associated with direct effects on brainstem structures. The transient nature of those changes suggests that aggressive intervention may not be needed. Maneuvers to limit the spread of papaverine to basal cisterns should be considered. (DOI: 10.3171/2011.6.JNS11183)

Key Words • papaverine • topical application • cerebral vasospasm • aneurysm clipping • vascular disorders

Papaverine, a potent cerebral vasodilator, is a useful drug for the treatment of cerebral vasospasm after subarachnoid hemorrhage. It can be administered in several forms including intraarterial, intravenous, oral, and topical, depending on the timing and location of the vasospasm. One of the most common uses of papaverine is as a topical solution to prevent or treat vasospasm during craniotomy. The exact mechanism of papaverine is not well understood, although it is thought to produce smooth muscle relaxation through cyclic guanosine monophosphate inhibition.7 There is some evidence that intraarterial papaverine also causes disruption to the blood-brain barrier.3

The use of topical papaverine for cerebral vasospasm has been associated with several adverse outcomes ranging from a transient unilateral dilated pupil to a fatal cardiac arrest.2,6,8 Cranial nerve dysfunctions have also been reported. Ipsilateral facial nerve palsy and auditory dysfunction have been described after intracisternal application of papaverine.1,4,5 One report described bilateral pupillary dilation after intracisternal application.1 The authors hypothesized that the transient mydriasis was a local effect on the oculomotor nerve based on the distribution of papaverine via CSF flow through the cisterns.

We report brainstem dysfunction after topical papaverine application in 2 patients who had globally diminished cortical somatosensory evoked potentials (SSEPs) following craniotomies for clipping of cerebral aneurysms.

Case Reports

Case 1

This 71-year-old woman presented with a diagnosis of transient bilateral brainstem dysfunction caused by topical application of papaverine.
of an unruptured 7-mm anterior communicating artery aneurysm. The patient had a resting tremor in the right upper extremity but otherwise normal neurological examination findings. She elected to undergo embolization of the aneurysm, which was not successful. The patient was then scheduled for a left craniotomy and aneurysm clipping.

In the operating room, general anesthesia was induced with thiopental and maintained with isoflurane, remifentanil, and vecuronium. An arterial line was used for invasive blood pressure monitoring. The patient was positioned supine with a roll under the left shoulder. The head was turned 45° to the right and secured with a Mayfield headholder.

During the craniotomy, the median and posterior tibial nerve SSEPs were used to monitor the patient. Evoked responses were unchanged throughout surgery during dissection and clipping of the aneurysm (Fig. 1). Prior to closing the dura, the surgeon applied topical papaverine (10 mg/ml) to the blood vessels in the surgical field. Within the next several minutes, the amplitudes of the cortical SSEPs decreased bilaterally for upper- and lower-extremity stimulation. Angiography performed during this period of SSEP decline demonstrated normal filling of the anterior communicating artery and other vessels as well as complete exclusion of the aneurysm. An arterial blood gas sample that was sent for examination immediately prior to the SSEP changes showed normal glucose, electrolytes, and carbon dioxide. The SSEP changes were communicated to the surgeon and, because of the findings on angiography and time course of events, no changes were made to patient management. An attempt was made to emerge the patient from anesthesia for a neurological examination. Upon conclusion of the surgery, the pupils were fixed and dilated bilaterally. The patient was unresponsive to deep painful stimulation in all 4 extremities but had an adequate spontaneous respiratory rate and tidal volume. An emergency CT angiogram was obtained for invasive blood pressure monitoring. The patient was transferred to the intensive care unit.

For the next 90 minutes prior to the SSEP changes, the patient remained normal throughout her hospital course. She was discharged from the hospital 10 days later with normal neurological examination findings.

Case 2

This 49-year-old woman with headaches was scheduled for a craniotomy and clipping of an 8-mm aneurysm at the right internal carotid artery bifurcation. Her neurological examination was normal in the preoperative anesthesia and neurosurgical clinics.

After induction of general anesthesia in the operating room, the anesthetic was maintained with propofol, isoflurane, remifentanil, and vecuronium. The position was comparable to the one described in Case 1. An arterial line was placed for blood pressure measurements.

As with the patient in Case 1, SSEPs to upper- and lower-extremity stimulation were monitored throughout the case and remained unchanged through completion of the clipping of the aneurysm (Fig. 3). Prior to closure of the wound, the surgeon applied topical papaverine (10 mg/ml) to several blood vessels in the vicinity of the clipped aneurysm. The amplitudes of the cortical SSEPs decreased globally within the next several minutes. The intraoperative angiogram demonstrated adequate filling of the patient's cerebral vessels without any filling of the aneurysm. After the SSEPs changes were noted, the surgeon requested that the mean arterial pressure be increased to 110–120 mm Hg. No changes were made to the anesthetic agents at this time. The patient had some gradual recovery of the SSEPs. At the conclusion of the operation about 90 minutes later, the patient emerged from anesthesia uneventfully and was successfully extubated.

Her neurological examination findings were normal and remained normal throughout her hospital course. She was discharged home 5 days later.

Discussion

These 2 cases suggest a direct neural effect of papaverine not only on the intracranial portion of cranial nerves but also on the brain itself. Anatomically, the somatosensory pathway is closest to the brain surface and nearest to the site of papaverine administration in the area of the medial lemniscus. Such an anatomical location of the observed effect is further supported by the bilateral mydriasis observed in the first case and would be consistent with spread of papaverine via the basal cisterns.

Although papaverine has been associated with cranial nerve dysfunction, hemodynamic changes, and blood-brain barrier disruption, to our knowledge direct effects on the brainstem have not been reported previously. The timing of SSEP changes shortly after topical papaverine use in the absence of changes to the anesthetic, surgical field, or blood flow are suspicious for a causal temporal relationship. The changes to the SSEPs were approximately equal bilaterally; therefore, an explanation for them must include either a systemic effect or bilateral local effects. The finding of bilaterally dilated pupils in the first patient localizes the anatomical location of the papaverine-induced SSEP changes to the upper brainstem and midbrain regions, an area where the sensory tracts run relatively superficial to the brain surface. Due to the proximity of the other cranial nerves, assessment of facial sensation and strength as well as hearing would have been of interest. Effects of papaverine on vestibulocochlear and facial nerves have been described.1–6

The timing of improvement of the SSEPs or neurological examination findings is also of interest. In Case 1, the patient did have a full recovery within 3–4 hours; in Case 2, the patient recovered within approximately 90 minutes. The difference in time to recovery may reflect differences in dose, sensitivity, or time to conclusion of the operation.
Brainstem dysfunction caused by topical application of papaverine

**Fig. 1.** Case 1. Somatosensory evoked potentials.  
**A:** Baseline recordings revealing normal and reproducible SSEP waveforms in response to lower- and upper-extremity stimulation. Paired traces are from the popliteal fossa, a cervical midline electrode, and contralateral cortical electrodes for posterior tibial nerve stimulation, and from Erb point, a cervical midline electrode and contralateral cortical electrodes for median nerve stimulation.  
**B:** Intraoperative recordings showing bilateral severe decreases in amplitude of the cortical responses without increases in latency. Papaverine was administered at the time indicated. To illustrate the time course of papaverine's effect, subsequent traces are labeled relative to the timing of papaverine.  
**C:** The electroencephalogram recorded from the cortical electrodes at the time of maximal SSEP depression.

**Fig. 2.** Case 1. Immediate postoperative CT and angiography.  
**Left:** Three-dimensional reconstruction of vessels in the posterior fossa. No inflow defects consistent with the widespread electrophysiological findings are evident.  
**Right:** Operative site and the associated vessels. Again, no obvious inflow deficits are apparent. A small frontal pneumocephalus was the only other significant finding on CT angiography.
In some case reports, damage to the cranial nerves has persisted for days or even months. One patient with a unilateral facial nerve palsy that occurred after a large dose of papaverine (240 mg) in the basal cistern recovered over a 2-month period. In another report, 2 patients with intraoperative changes to the brainstem auditory evoked potentials after papaverine had postoperative dizziness and hearing loss. Although one patient demonstrated a full recovery at 3 months, the other patient had persistent dizziness at the 15-month follow-up. Although these are striking results, stretch-induced injury to these cranial nerves during the operation must be considered as an alternative explanation for the persistence of this finding.

It is unknown whether papaverine could cause persistent brainstem changes. Since SSEPs were not recorded in the intensive care unit, we are unable to document the full time course of recovery of the SSEPs. On the other hand, the neurological examination findings were grossly normal in both patients after extubation, suggesting that they both had a full recovery from the intraoperative SSEP changes. It is unlikely that residual general anesthesia could have masked any persistent major neurological deficits, although it is theoretically possible that subtle residual deficits could have been present. Even though the attribution of the observed neurological findings to papaverine administration is circumstantial, the transient nature of these findings suggests that aggressive intervention may not be warranted.

The mechanism of any possible brainstem effects of papaverine remains elusive. Although disruption of the blood-brain barrier by intraarterial papaverine has been reported, the clinical implications of this are not clear. In our 2 patients, the papaverine was applied topically to relieve vasospasm. Regardless of the mechanism whereby papaverine disrupts neuronal function, our cases suggest that papaverine readily penetrates into neural tissues. Maneuvers to limit the spread of papaverine to basal cisterns such as administering it via soaked pledgets may be helpful in limiting the spread.

**Disclosure**

Dr. Peters is on the Speakers Bureau for Toshiba America Medical Systems.

Author contributions to the study and manuscript preparation include the following. Conception and design: Seubert, Mahla, Lewis. Acquisition of data: Seubert, Mahla, Reichwage, Lewis,
Brainstem dysfunction caused by topical application of papaverine

Peters. Analysis and interpretation of data: Seubert, Moran, Mahla, Lewis, Peters. Drafting the article: Seubert, Moran. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Seubert. Administrative/technical/material support: Seubert, Moran.

References