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CLINICAL ARTICLE

Adverse effects of topical papaverine on auditory nerve function

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Abstract
Background Papaverine hydrochloride is a direct-acting vasodilator used to manage vasospasm during various neurosurgical operations. Transient cranial nerve dysfunction has been described in a few cases with topical papaverine. This study supports previous reports and provides neurophysiological evidence of an adverse effect on the auditory nerve.
Methods We conducted a retrospective review of 70 consecutive microvascular decompression operations and studied those patients who received topical papaverine for vasospasm. Topical papaverine was used as a direct therapeutic action to manage vasospasm in a total of 11 patients. The timing of papaverine application and ongoing operative events was reviewed relative to changes in neurophysiological recordings. Brainstem auditory evoked potentials (BAEPs) were routinely used to monitor cochlear nerve function during these operations.
Findings A temporal relationship was found between topical papaverine and BAEP changes leading to complete waveform loss. The average temporal delay between papaverine and the onset of an adverse BAEP change was 5 min. In 10 of 11 patients, BAEP waves II/III–V completely disappeared within 2 to 25 min after papaverine. Eight of these 10 patients had complete loss of BAEP waveforms within 10 min. One patient showed no recovery of later waves and a delayed profound sensorineural hearing loss. The average recovery time of BAEP waveforms to pre-papaverine baseline values was 39 min.
Conclusions Topical papaverine for the treatment of vasospasm was associated with the onset of a transient disturbance in neurophysiological function of the ascending auditory brainstem pathway. The complete disappearance of BAEP waveforms with a consistent temporal delay suggests a possible adverse effect on the proximal eighth nerve. Recommendations to avoid potential cranial nerve deficits from papaverine are provided.

Keywords Auditory · Brainstem · Decompression · Evoked potentials · Intracranial · Papaverine · Surgical · Vasospasm

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Introduction

Topical application of papaverine hydrochloride was first described to treat cerebral vasospasm during neurosurgical operations in 1958 [24]. This potent vasodilator has a rapid onset of action and relatively short pharmacologic duration of action. Despite a poorly understood mechanism of action, papaverine is used today to manage vasospasm caused by arterial manipulation and subarachnoid hemorrhage. Topical papaverine is used to treat complications related to vasospasm during microvascular decompression [30] and other posterior fossa operations [27]. During vestibular schwannona resection, topical papaverine is used to prevent vascular insufficiency to the inner ear and improve hearing outcome [4, 21]. Experimental evidence to support a therapeutic effect of papaverine on cochlear blood flow is limited [20, 23].

Several reports suggest that papaverine may cause adverse effects lasting hours to days [14, 18, 29]. Potential reactions are diverse and include transient neurological dysfunction, increased intracranial pressure,

brainstem depression, seizures, hemodynamic changes, paradoxical reactions, thrombocytopenia, and precipitation of the drug from solution [3, 5, 6, 8, 12, 15, 19, 26]. Selective gray matter changes in the territory of papaverine infusion may suggest a permanent neurotoxic effect [28]. Topical papaverine seems to have relatively moderate effects compared to intraarterial and intracisternal infusions that may lead to more severe reactions. Cranial nerve dysfunction has been described in a few cases with topical papaverine [7, 11]. Transient mydriasis after papaverine administration is well known [2, 10, 25].

The purpose of this report was to describe a possible effect of topical papaverine on auditory nerve function. Papaverine was used as a direct therapeutic response to arterial vasospasm during microvascular decompression in our practice. Since the proximal eighth nerve was exposed during intradural decompression and within the field of papaverine, it may be susceptible to a transient adverse reaction similar to other cranial nerves.

Methods and materials

Patients

A series of 70 patients who underwent a suboccipital craniectomy for microvascular decompression during an 11 year period at a single institution was retrospectively reviewed. In the series, topical papaverine was used to treat vasospasm in 11 cases. Of these, six patients were diagnosed with trigeminal neuralgia and five with hemifacial spasm. Ages ranged from 45 to 81 years. There were six males and five females. This was the first microvascular decompression operation for all 11 patients, with the exception of a single patient who underwent a second procedure for recurrent trigeminal neuralgia. Brainstem auditory evoked potentials (BAEPs) were used to monitor auditory nerve function during all microvascular decompression operations. Waiver of informed consent and individual authorization was obtained from the Institutional Review Board of Carolinas HealthCare System (Charlotte, NC, USA).

Papaverine hydrochloride

Papaverine hydrochloride injection, USP, 30 mg/mL, with 0.5% chlorobutanol (chloroform derivative), 1 to 2 mL single dose (Ben Venue Laboratories, Inc., Bedford, OH, or American Regent Laboratories, Inc., Shirley, NY, USA) was used as a direct therapeutic action to vasospasm. Under visualization with the operating microscope, papaverine was slowly released through the tip of a 21-gauge angiocath, and applied topically to the vessel(s) in spasm. A clinical decision to treat vasospasm with papaverine was made by the neurosurgeon when external narrowing of the lumen significant enough to compromise blood flow was seen microscopically. Papaverine was not used in response to any BAEP change associated with cerebellar retraction or arachnoid dissection. It was not added to lactated Ringer's solution because precipitation may result. One patient with hemifacial spasm had two doses of papaverine approximately 3 min apart.

Results

Pertinent operative findings related to vasospasm are summarized in Table 1.

Papaverine had an excellent therapeutic response as vasospasm resolved promptly within seconds. Focal spasm of the internal auditory artery occurred in two patients. In a third patient, the internal auditory artery appeared to emanate from the upper portion of the vessel in spasm. In another patient, papaverine was applied over the vessels that were dissected away from the facial nerve, including a vessel that probably was the internal auditory artery. In the seven remaining patients, three had vasospasm of the superior cerebellar artery (SCA), one of the SCA and/or anterior inferior cerebellar artery (AICA), one of a small branch of the AICA, one of the basilar artery, and one of an unknown vascular loop.

Brainstem auditory evoked potential changes associated with topical papaverine are shown in Table 2. In 10 of 11 patients, BAEP waves II/III–V completely disappeared within 2 to 25 min after local papaverine irrigation. Eight of the 10 patients had complete loss of BAEP waveforms within 10 min. The two remaining patients with complete loss of BAEP waveforms later than 10 min, showed a significant decrease in amplitude of BAEP waves II–V at 2 and 6 min, respectively. Six of nine patients with adverse BAEP changes following papaverine showed wave II involvement. Three patients had retrograde BAEP wave I amplitude and/or latency changes.

Two patients with hemifacial spasm reported immediate postoperative auditory or vestibular problems. In the first patient, a large branch of the AICA split the VII/VIIIth nerve complex and gave off the labyrinthine artery deep in the edge of the porus. Focal spasm of the internal auditory artery coincided with a marked amplitude decrease in BAEP waves III–V. Three minutes after papaverine however; BAEP waves II–V completely disappeared. Postoperative complaints included decreased hearing, tinnitus, dizziness, and balance difficulty. An audiogram at 4 months revealed normal hearing in the operative ear with the exception

Table 1 Clinical characteristics and operative findings in eleven patients with topical papaverine irrigation for vasospasm[a]

Case no.	Operative findings	Cerebellar retraction	Papaverine irrigation for vasospasm	Postoperative findings	Clinic follow-up
1	Loop of SCA wrapped around inferior part of CN5 and embedded medially, another vascular loop (probably AICA) embedded within the medial aspect of CN5	Retractor removed with BAEP wave V decrease while removing arachnoid around 5CN	Papaverine irrigation for slight spasm of inferior vessel that was removed from the nerve, warm saline irrigation	No facial pain, mild hypesthesia in V2 distribution	No facial pain, mild hypesthesia in V2 distribution
2	Loop of AICA coursing upward toward REZ of nerve complex, pledget placed between the arterial loop inferiorly and the 7/8CN complex, small pledget placed over the 7/8CN complex to separate the internal auditory artery away from the nerve	Retractor removed with BAEP wave V decrease and internal auditory artery spasm	Papaverine irrigation with small amount of internal auditory artery spasm	Few residual spasms, transient facial weakness, improving vertigo, tinnitus	No residual spasms, very mild residual facial weakness, mild horizontal nystagmus, improved vestibular symptoms, decreased hearing
3	Large branch of AICA split the 7/8CN and gave off the labyrinthine artery deep in the edge of the porus, unable to decompress 7/8CN complex completely, sponge placed between two nerves	Retractor removed with BAEP wave V decrease during vessel exposure	Focal spasm of labyrinthine artery, irrigation with papaverine and warm saline	Slight facial twitching in lower face, some facial weakness, tinnitus, hearing grossly intact	Decreased facial spasms (2–3 per month), tinnitus, decreased hearing, dizziness, disequilibrium, some tic douloureux
4	7CN compressed in three locations, large vascular loop, small vein, and artery that may be branch of internal auditory artery extending up between 7/8CN and extending into the IAC	Retractor removed after sponge placement	Papaverine irrigation over vessels that were dissected away from nerve, and after sponge placement	Facial spasms improved	Complete relief of facial spasm
5	5CN compressed in two locations by branch of SCA	Retractor removed with BAEP wave V decrease after sponge placement	Papaverine was left on vessel for approximately 5 min	No facial pain	No facial pain
6	Two loops of SCA appeared to be indenting the inner and upper aspects of CN5, and these were displaced superiorly	Retractor removed with BAEP wave V decrease during arachnoid dissection, retractor replaced for 2 min during sponge placement because fuller visualization was needed, and associated with BAEP wave V decrease during sponge placement	Papaverine irrigation after sponge placement of one of the SCA loops that appeared somewhat constricted, retractors already out	Good improvement in facial pain however; some mild occasional breakthrough pain	Return of lancinating pain
7	Large ectatic basilar and SCA complex compressed 5CN, some slightly increased pressure placed on 6CN because of displacement of the basilar artery	No changes in cerebellar retraction, BAEP stable	Papaverine irrigation 12 min after sponge placement for basilar artery spasm, retractors already out	Partial 6CN palsy causing some double vision	No facial pain, small residual 6CN palsy, mild diplopia, some balance problems, delayed hearing loss

Table 1 (continued)

Case no.	Operative findings	Cerebellar retraction	Papaverine irrigation for vasospasm	Postoperative findings	Clinic follow-up
8	Several vascular structures compressing 5CN, loop of SCA lightly compressing undersurface of nerve, AICA significantly compressing medial aspect of nerve, and large venous structure	Retractor removed after sponge placement	Papaverine irrigation after sponge placement, retractors already out	Complete relief of facial pain, some lower facial numbness primarily in V2 distribution	Complete relief of facial pain; sensitivity to loud sounds; some numbness in V2/3 distribution; occasional aural fullness
9	Vascular loop against the undersurface of CN7/8 complex that was actually causing compression of CN7, the internal auditory artery appeared to be emanating from the upper portion of the loop and went into the IAC	Retractor removed during the final part of the microdissection with marked BAEP change	Papaverine irrigation after sponge placement, some spasm in the vascular loop, papaverine was allowed to sit for several minutes and then was irrigated out	Mild persistent facial spasms, but overall greatly improved, mild facial weakness	Facial spasms markedly diminished however; symptoms recurred at 1 month
10	Scarred arachnoid dissected from REZ, scarred arterial loop (probably SCA) 4 mm distal to REZ, and large vein coursing along the nerve	Retractor repositioned and removed with BAEP wave V amplitude decrease during dissection of arachnoid from nerve	Papaverine irrigation and probable vasospasm, retractors already out	Mild lower facial numbness	No facial pain, some numbness in V2/V3 distribution (arterial loop was scarred into the nerve and dissected off)
11	A dolichoectatic vertebral artery and branch of AICA embedded in the lateral portion of the brainstem and obscuring the REZ of the VIIth and VIIIth nerves	Retractor removed with BAEP wave V decrease after sponge placement	Papaverine irrigation for spasm of a small branch of AICA with warm Bacitracin solution after sponge placement	Facial spasms resolved, mild facial weakness progressed to complete facial palsy	No facial spasms, evacuation of persistent frontoparietal subdural hematoma

[a] *AICA* anterior inferior cerebellar artery, *BAEP* brainstem auditory evoked potential, *CN* cranial nerve, *IAC* internal auditory canal, *MVD* microvascular decompression; *REZ* root entry zone; *SCA* superior cerebellar artery

of a mild (40 dB) loss at 250 Hz, and an excellent (100%) word recognition score. Dizziness and balance problems persisted at 15 months follow-up.

In the second patient, a loop of the AICA was found to course upward toward the root entry zone of the VII/VIIIth nerve complex. Slight vasospasm of the internal auditory artery closely coincided with marked attenuation of BAEP wave V amplitude. Topical papaverine was applied and cerebellar retraction was removed a minute later. Five minutes after papaverine however; BAEP waves II–V completely disappeared. Postoperative complaints included tinnitus, vertigo, and hearing loss. An audiogram at 5 weeks revealed a unilateral steeply sloping moderate to severe sensorineural hearing loss at 1,500 Hz through 8,000 Hz, with a poor (32%) word recognition score. Hearing was within normal limits for the non-operative ear. At 3 months follow-up, vestibular symptoms were greatly improved, but hearing sensitivity remained unchanged.

Illustrative cases

Patient one

Radiographic imaging showed a tortuous basilar artery compressing the right trigeminal nerve root entry zone in an 80 year old male (Fig. 1). The nerve was sandwiched between branches of the SCA and AICA, and draped over the basilar. Twelve minutes after sponge placement, topical papaverine was applied for basilar artery spasm (retractors removed 6 min earlier). Two minutes later, previously stable BAEP waves II–V completely disap-

peared and wave I showed a markedly prolonged latency with broadened slope (Fig. 2). There was no subsequent recovery of the BAEPs, and waves II–V remained completely absent. No qualitative change in hearing function was reported postoperatively.

Patient two

Three sources of compression were identified at the root entry zone of the facial nerve in a 47 year old male; a large vascular loop, a small vein, and a small artery that probably was a branch of the internal auditory artery. Topical papaverine was applied for vasospasm 2 min after sponge placement. Previously stable BAEPs showed slightly attenuated waves II–V 2 min later (Fig. 3). At 4 min post-papaverine, waves II–IV were no longer identifiable, and wave V was attenuated and prolonged. Cerebellar retractors were removed 8 min after papaverine, and waves II–V completely disappeared 13 min later. Twenty-nine minutes after papaverine, waves II–V reappeared, and gradually improved to pre-papaverine levels 10 min later.

Discussion

Previous studies have reported transient cranial motor nerve dysfunction following topical application of papaverine. Transient mydriasis after papaverine administration during craniotomy for an aneurysm clipping is a known adverse reaction. Although papaverine was delivered intracisternally in these cases, the method of application was topical. McLoughlin [18] reported a constellation of side effects with intracisternal papaverine including a dilated, unreactive pupil and eyelid lag. Pupillary changes were previously reported by Pritz [25] in three patients with a fixed and dilated pupil on the operative side lasting 2 to 4 h after intracisternal papaverine despite no oculomotor nerve manipulation during aneurysm clipping. A commentary to that article reported a case of bilaterally and fixed pupils lasting 4 days after papaverine irrigation of the internal carotid artery and adjacent vessels during aneurysm clipping [2]. Although the ipsilateral oculomotor nerve was decompressed in this case, surgical trauma could not explain the contralateral deficit since the contralateral nerve was never exposed. Lang et al. [11] reported combined

Table 2 Demographic characteristics in eleven patients who underwent microvascular decompression and BAEP changes associated with topical papaverine[a]

Case no.	Diagnosis	Baseline BAEP	BAEP before papaverine	BAEP after papaverine	Onset of BAEP change after papaverine	Return to pre-papaverine BAEP	Final BAEP
1	TN	Normal	Delayed wave V latency; waves I–IV already lost	Wave V lost	8 min	55 min	Abnormal
2	HS	Normal	Waves IV/V markedly attenuated	Waves II–V lost	5 min	42 min	Abnormal
3	HS	Normal	Waves III–V decreased	Waves II–V lost	3 min	85 min	Abnormal
4	HS	Borderline	No significant change	Waves II–V lost	Waves II–V decreased at 2 min; lost at 21 min	39 min	Baseline
5	TN	Normal	Prolonged latency/ markedly decreased amplitude waves III–V	Same	No further adverse BAEP change	Not applicable	Baseline
6	TN	Abnormal	Waves II–V decreased	Waves II–V lost	10 min	23 min	Abnormal
7	TN	Abnormal	No significant change	Prolonged wave I latency; waves II–V lost	2 min	No BAEP waves II–V return at 35 min	Abnormal
8	TN	Normal	Waves II–V decreased	Waves III–V lost	2 min	7 min	Abnormal
9	HS	Borderline	Waves III–V decreased	Waves III–V lost	6 min	8 min	Abnormal
10	TN	Normal	Wave V decreased	Waves III–V lost	6 min	45 min	Baseline
11	HS	Normal	Delayed III–V latencies with decreased amplitudes	Waves II–V lost; wave I amplitude attenuated	Waves I–V attenuated at 6 min; waves III–V lost at 13 min; waves II–V lost and wave I attenuated at 25 min	50 min	Abnormal

[a] *BAEP* brainstem auditory evoked potential, *HS* hemifacial spasm, *TN* trigeminal neuralgia

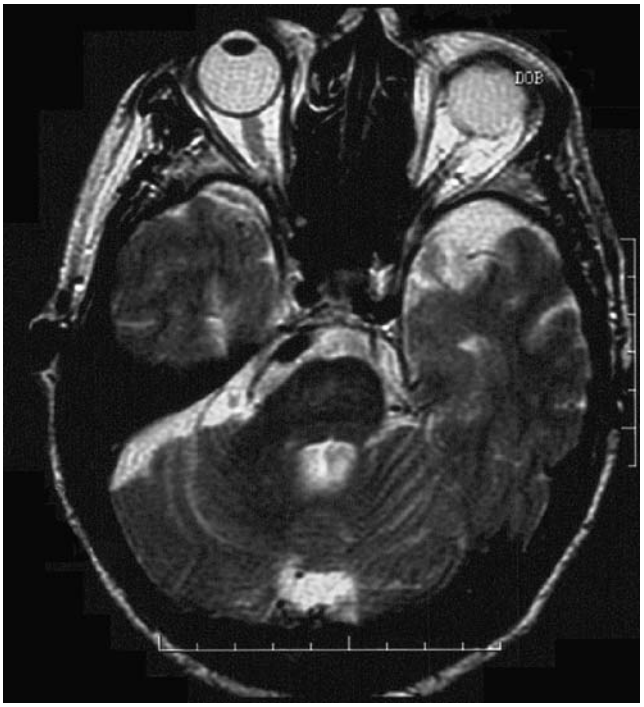

Fig. 1 Preoperative magnetic resonance imaging study showing an ectatic basilar artery compressing the root entry zone of the right trigeminal nerve in Patient One

oculomotor and facial nerve dysfunction following papaverine application during craniotomy for clipping of a middle cerebral artery aneurysm. Pupillary dilation and areflexia lasted 90 min, however a prolonged House-Brackmann Grade IV facial nerve paresis did not fully recover until 2 months later.

Topical application of papaverine has been associated with temporary facial nerve palsy during translabyrinthine craniotomy for vestibular schwannoma resection. Eisenman et al. [7] reported reversible conduction block of the facial nerve with topical papaverine to relieve vasospasm of a branch of the AICA. Both spontaneous and evoked facial muscle activity were completely lost within seconds after papaverine irrigation in the cerebellopontine angle (CPA). After tumor removal, electrical stimulation at the porus acousticus produced facial motor activity, whereas no activity was elicited to stimulation at the brainstem. These findings suggest intraoperative facial nerve conduction block proximal to the porus. Facial paralysis resolved within 12 h postoperatively.

Postoperative auditory dysfunction

Two patients with papaverine therapy in our series reported decreased hearing immediately postoperatively. Audiological findings in the first patient were normal with the exception of a single mildly elevated low frequency threshold, whereas a moderate to severe high-frequency sensorineural hearing loss was found in the second. Focal spasm of the internal auditory artery in this later case coincided with marked BAEP wave IV/V attenuation. Vasospasm of the internal auditory artery or the occurrence of vasospasm within the nerve may cause ischemia and alter BAEPs [21]. The temporal delay associated with topical papaverine and the subsequent adverse BAEP change was consistent with our other cases, although this was the only case of significant hearing loss immediately after surgery.

A delayed profound sensorineural hearing loss of unknown etiology occurred in one patient 2 months postoperatively. Brainstem auditory evoked potentials were stable in this case until topical papaverine was applied for vasospasm of the basilar artery (Patient One). Despite the presence of a delayed BAEP wave I with absent later waveform components, no qualitative change in hearing function was noted postoperatively. Delayed profound sensorineural hearing loss was similarly reported by McDonnell et al. [16] following microvascular decompression of a large ectatic vertebrobasilar artery.

Our experience suggests that topical papaverine is a significant contributor to BAEP waveform changes. In Patient One, the acute BAEP loss 2 min post-papaverine was probably not the result of auditory nerve stretch or trauma as sponge placement and removal of cerebellar retraction preceded the acute BAEP change by 12 and 6 min, respectively. Vasospasm of the basilar artery could cause BAEP changes, but the onset of waveform changes did not coincide with the onset of vasospasm. Dura closure had not begun, so replacement of cerebrospinal fluid as a possible source of VIIIth nerve tension from the implant or displaced vessel would be unlikely [17]. Presence of a delayed BAEP wave I with absent later components post-papaverine suggests an auditory nerve or vascular disturbance. In Patient Two, BAEPs remained stable until 2 min post-papaverine. The complete disappearance of BAEP waves II–V with an intact wave I suggests a proximal eighth nerve disturbance. Although a displaced vessel or pledget could somehow impinge the auditory nerve, BAEPs gradually improved with no re-exploration of the decompression or eighth nerve.

Since the ascending auditory pathway is relatively lateral and posterior in the brainstem, papaverine-induced brainstem ischemia and resultant BAEP changes are possible. Topical papaverine could possibly reach the cochlear nucleus since it is located partially on the surface of the brainstem at the pontomedullary junction. However, none of our patients exhibited any clinical signs of brainstem ischemia postoperatively. A direct effect of papaverine on the brainstem and central nervous system has previously been suggested [1, 3]. This pharmacologic effect could be enhanced by locally diminished cerebral blood flow secondary to vasospasm.

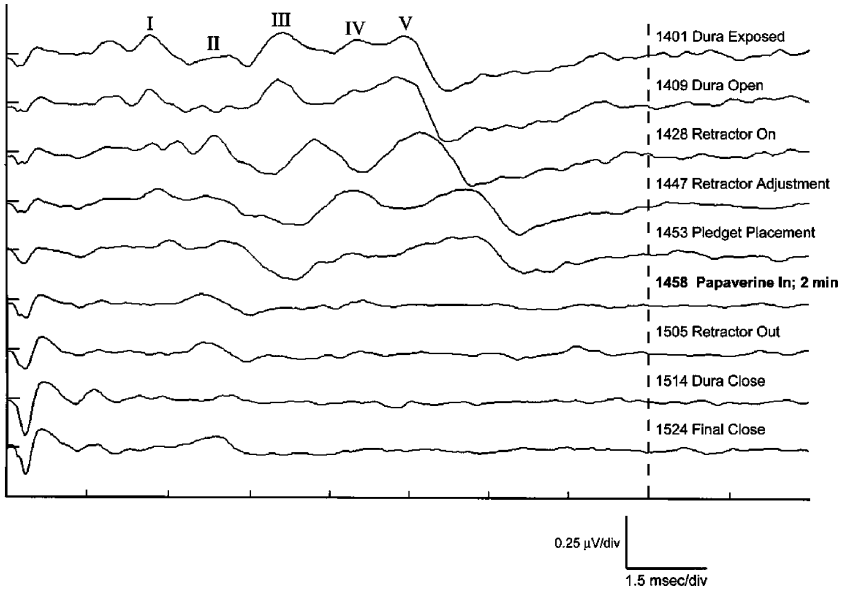

Fig. 2 Intraoperative BAEP recordings (ipsilateral ear) during trigeminal nerve decompression depicting timing of topical papaverine and associated operative events in Patient One

Vasospasm and BAEPs

Focal spasm of the internal auditory artery coincided within seconds of an acute decrease in BAEP wave V amplitude. When the internal auditory artery emanated from the vasospastic vessel, BAEP changes were similar. In one case, vasospasm was noted in a small branch of the AICA that was pressed into the facial nerve by a dolichoectatic vertebral artery. Since the vertebrobasilar system is the origin for the AICA and its collaterals, including the internal auditory artery, these findings were not unexpected. Arterial narrowing of the internal auditory artery may reduce cochlear nerve perfusion and alter BAEPs. In contrast, there was a consistent temporal delay between topical papaverine and further adverse BAEP changes leading to complete waveform loss. Although vasospasm probably contributed to the initial BAEP waveform change, papaverine seemed to have a further adverse effect. Recovery of BAEP waveforms did not occur when vasospasm of the internal auditory artery was no longer visible. Recovery of synchronized neural activity necessary for BAEP waveforms may take longer to occur.

Mechanism

Transient changes in cranial nerve function may represent a neurotoxic effect of papaverine. Chlorobutanol, the preservative in papaverine, may be contributory [22], but we are unaware of any synergistic effect. Hendrix et al. [10] proposed that papaverine may act directly on the muscula-

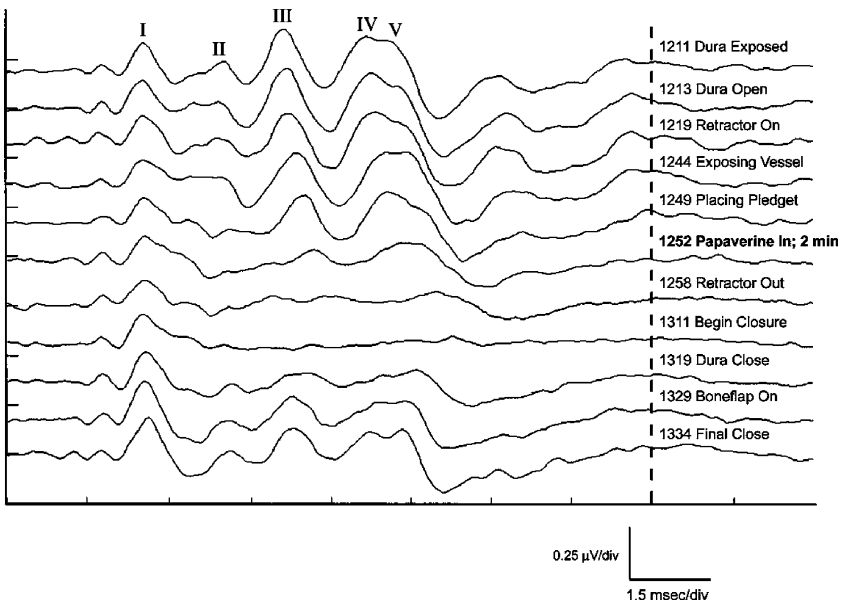

Fig. 3 Intraoperative BAEP recordings (ipsilateral ear) during facial nerve decompression depicting timing of topical papaverine and associated operative events in Patient Two

ture of the iris to produce pupillary dilatation. Animal studies suggest that the spasmolytic action of papaverine may interfere with the influx of calcium ions during muscle contraction [13]. As suggested by Lang et al. [11], the degree of depolarization may be a factor since the potency of papaverine is influenced by the influx of calcium ions. Eisenman et al. [7] described the reaction of the facial nerve as analogous to a peripheral conduction delay from a local anesthetic. The authors proposed that papaverine, as an opioid-derivative, may act as a local anesthetic and influence the excitability of nerve fibers. Local anesthetics and calcium ions are considered stabilizers and act to decrease nerve excitability [9].

Another factor contributing to decreased neural activity may be related to the pH of papaverine. According to information provided on the Material Safety Data Sheets (MSDS) from our two pharmaceutical manufacturers, the pH level of papaverine ranged from 3.0 to 3.8. Papaverine has a much lower pH relative to blood and intracerebral fluid, and is therefore relatively acidic. Most neurons are highly responsive to changes in pH [9], and BAEPs are highly dependent on synchronized neural activity.

If papaverine acts as a local neurotoxic agent, the outermost fibers of the eighth nerve would preferentially be affected. The cochlear nerve may be specially vulnerable, since the transition zone between peripheral and central myelin is located just inside the porus. Delayed onset of papaverine-induced BAEP changes may reflect a progressive action and the signal averaging process. The average recovery period of 39 min for BAEP waveforms to pre-papaverine levels was comparable with the time course of effects on other cranial nerves cited earlier. Previous reports of adverse effects on cranial nerve function with topical papaverine have been observational. Strength of our study includes the timing of papaverine relative to a measurable change in neurophysiological function. However, as with other studies, an interaction with local changes in blood flow secondary to vasospasm may be a possible confounding variable.

Conclusion

Until the neuropathic effect of papaverine hydrochloride is better understood, we recommend keeping this agent away from the proximal eighth nerve to avoid complications in auditory function. Dilution of papaverine in saline prior to application is recommended. To control the spread of papaverine, it may be advantageous to place a small papaverine-soaked Gelfoam pledget against the spastic segment until the spasm resolves. It is our practice to avoid using this agent unless severe vasospasm is observed.

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Comment

The authors of this retrospective study should be acknowledged for bringing attention of the neurosurgical community to the potential dangers of cisternal and/or topical application of Papaverine.

We share with Geraldine M Chadwick and coworkers the same practical experience. Since our training with Prof Gazi Yasargil in Zurich in the seventies, we have been using local application of Papaverine along and at the end of our surgeries, especially the ones dealing with aneurysms, skull base tumours and microvascular decompression. At the beginning of our experience we tended to widely irrigate the cisterns with Papaverine (at a dilution of 1ml in 10ml of Ringer's solution). We rapidly noticed (not rare) occurrence of side-effects as those mentioned in this well documented article, with the addition of - otherwise unexplained - epileptic focal seizures as soon as the patient awoke. In order to try to explain these harmful effects, as well as the rapid vasodilatation action of the Papaverine, we asked the chemical laboratory to measure the PH of the solution; it was found at 2.8. So, we found logical to hypothesize that a strong and acute acidose effect on vessels and neural tissue are the main agent of vasodilation and of neural (hopefully transient) toxicity. Because of its beneficial effects to prevent ischemia related to vasospastic "reflexes" after manipulating arteries, we did not abandon Papaverine along surgeries, but only used it in limited topical application with some droplets directly and selective put on the targeted vessels under the microscope (ref 2). While performing microvascular decompression at the VIIth - VIIIth cranial nerves, we could observe soon after application of Papaverine same wave depressions as the ones described in this article when Papaverine was used "in excess", but also - conversely- reversal of decrease in amplitude of peak I linked to vasospasm of AICA or labyrinthine artery when applied topically, and saving the patient from hearing loss (ref1).

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