CASE REPORT

Peripheral Sympathectomy as a Novel Treatment Option for Distal Digital Necrosis Following Parenteral Administration of Promethazine

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Abstract Promethazine is a commonly used medication to treat nausea and motion sickness. Case reports have recently surfaced on the dangers of parenteral administration of promethazine. We present a case report of a presumed intravenous injection of promethazine into an antecubital intravenous line resulting in necrosis of the ring finger distal to the DIP joint and hypoperfusion of the digits. Peripheral sympathectomy was performed to improve nutritional flow and improve ischemic pain. However, although this novel treatment option was successful, ultimately the patient had an amputation of her ring finger at the level of her middle phalanx. Although no proven successful treatment exists, the updated treatment options following inadvertent intra-arterial or perivascular administration are presented. Given the limited success of current treatment options for intra-arterial or perivascular extravasation, the staggering medical malpractice awards in such cases, and the numerous therapeutic alternatives to promethazine, the medical community should question the safety and continued administration of promethazine by an intravenous route.

Introduction

Although promethazine is a commonly used and effective antiemetic, its safety profile has recently been questioned as its use has led to more adverse drug events than all the other antiemetics combined [9, 11]. In particular, reports of distal digital necrosis following inadvertent intra-arterial injection in the upper extremity or following extravasation in

the antecubital fossa have been published since the 1960s [1–3, 6–8].

Unfortunately, no treatment has been proven to be successful for treating unintentional intra-arterial injection or perivascular extravasation. Treatment considerations in the acute phase include sympathetic blockade (stellate ganglion), limb elevation, local anesthetic infiltration to promote vasodilation, and heparinization (i.e., anticoagulation) [2, 6]. Other treatment options that have been suggested include high-dose steroids, intra-arterial vasodilators, hyperbaric oxygen therapy, and nitropaste (or other topical vasodilators) [6, 10]. Arterial spasm can further be managed by calcium channel blockers, papaverine, thorazine, local anesthetic injections, and thromboxane inhibitors. If indicated, thrombolytics can be considered. However, despite the use of nonsurgical interventions, surgery is often needed including fasciotomy, amputation, and skin grafts.

Promethazine is known vesicant with a pH between 4 and 5.5 and is highly caustic to the intima of blood vessels and surrounding tissue. Inadvertent intra-arterial or subcutaneous administration results in significant complications including severe spasm of vessels, thrombophlebitis, venous thrombosis, tissue necrosis, and gangrene. In general, patients with vascular damage and vasospasm do not respond well to medical therapy [4]. Sympathectomy in this scenario is hypothesized to improve digital flow both by sympathetic denervation and by removal of external compression caused by the noncompliant periadventitial fibrosis. Although digital sympathectomy is the commonly used term for the procedure, other authors have highlighted the importance of external decompression of the arteries by labeling the procedure as “adventitial stripping” or “decompression arteriolysis” [5, 12]. The following case is the first report of distal digital necrosis caused by promethazine that was successfully treated with peripheral sympathectomy.

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Fig. 1. Clinical photograph showing distal digital necrosis of the fourth digit, distal to the DIP joint, and mottling of digits one to three

Case Report

An 82-year-old right hand-dominant female presented to an outside institution for a carotid endarterectomy (CEA). A radial arterial line was placed in the patient's right wrist for monitoring, and a large-bore intravenous line was placed in her right antecubital fossa. Following an uneventful operation, she developed nausea on the day of surgery and was given a single dose of promethazine by intravenous push through the large-bore line in her antecubital fossa. Although the antecubital site of administration was confirmed

by the patient and nursing reports, the intravenous as opposed to inadvertent intra-arterial placement of the antecubital catheter cannot be confirmed in retrospect. Immediately after administration, the patient developed extreme pain in her hand and digits, equating the pain to "a bomb going off in [her] hand." Over the subsequent 24 h, she experienced continued pain with dysesthesias in her right thumb, middle and ring fingers, and she developed severe swelling in her right hand and forearm. No further diagnostic studies were performed, but in the setting of progressive dysesthesias and marked swelling, she underwent right carpal tunnel release 2 days after the promethazine injection without improvement in her symptoms. She had been treated with aspirin and Plavix following the CEA, but no additional anticoagulation or thrombolytic agent was utilized. A calcium channel blocker, nifedipine, was prescribed by the outside treating physician, presumably to improve vascular flow and/or to treat vasospasm through vasodilation, and she was referred to occupational therapy, presumably to prevent stiffness in the hand. Four days after her CEA, she was discharged home with improved swelling, but continued pain, dysesthesias, dry gangrene of the tip of the ring finger at the level of the distal interphalangeal (DIP) joint, and mottling of all her digits excluding the small finger.

She presented to our office on postoperative day 5. Physical examination revealed a well-healing incision from her carpal tunnel release without signs of infection. No swelling was noted in the forearm or hand. She had dry gangrene and numbness of the tip of the ring finger at the level of the DIP joint, mottling of all her digits excluding the small finger, and dysesthesias in her thumb and middle finger (Fig. 1.). Her radial pulse was palpable, and her ulnar artery had a Doppler signal in the forearm and just proximal to the wrist. Doppler signals were present in the second, third, and fourth common digital arteries with an abnormal monophasic signal in the fourth interspace. With occlusion of the radial artery at the

Fig. 2. Pulse volume recordings demonstrating severely diminished PPG waveforms, indicative of severely diminished perfusion in the right first, third, and fourth digits

Fig. 3. Two-dimensional noncontrast time of flight MRA showing flow-related enhancement of radial, ulnar, and posterior interosseous arteries throughout the forearm with radial artery dominance at the wrist

wrist, the Doppler signals in all common digital arteries were lost. She was sent for immediate pulse volume recordings and a magnetic resonance arteriogram (MRA) of the wrist and forearm. Pulse volume recordings showed severely diminished photoplethysmography (PPG) waveforms, indicative of severely diminished perfusion in the right first, third, and fourth digits (Fig. 2.) MR angiography was performed utilizing initial two-dimensional noncontrast time of flight techniques, followed by contrast-enhanced time intensity sensitive gradient-recalled sequencing. MRA showed flow-related enhancement of the radial, ulnar, and posterior interosseous arteries throughout the forearm with radial artery dominance and a thin, attenuated ulnar artery at the wrist (Fig. 3). The radial artery formed a portion of the deep palmar arch with poor reconstitution of the ulnar margin of the deep arch through collateral vessels. The superficial arch was not intact, and the princeps pollicis branch was markedly attenuated. In addition, marked attenuation of digital flow to all digits was apparent with severely compromised flow through the radial and ulnar digital arteries of the ring finger. The hand was extensively warmed during imaging in an effort to minimize physiologic vasospasm occurrence because of the extremity being in a cold environment during the MRA. Given her delayed presentation with marked pain, nonsalvageable dry gangrene of the ring finger tip, and severely diminished perfusion of the thumb and middle finger placing viability of these digits at risk, a peripheral sympathectomy was recommended to improve nutritional flow and improve ischemic pain.

Surgery was performed under regional anesthesia using an infraclavicular block. A tourniquet was applied to the right upper extremity and inflated to 250 mmHg. Peripheral sympathectomy was performed on the ulnar and radial arteries just proximal to the wrist using two longitudinal incisions directly over the arteries and stripping adventitia over a length of 2 cm for each artery. Sympathectomy of the superficial arch and deep arch, in addition to the common digital arteries, was then performed via a T-shaped incision in the palm. Intraoperatively, she was found to have significant periadventitial thickening and fibrosis of the deep and superficial arches and around all common digital arteries with a component of extravascular tissue involvement. In addition, she had a visible occlusive thrombus in the common digital artery in the fourth

interspace. A revascularization procedure or thrombectomy was considered but not performed given the established and demarcated necrosis of the tip of the ring finger at the DIP joint. The tourniquet was deflated, and flow, color, and temperature of all digits were significantly improved compared to preoperative exam. The incision was closed using simple sutures. Postoperative management included a Bair Hugger® (Arizant, Eden Prairie, MN) to keep the hand warm, an infraclavicular catheter for 24 h, and continued use of Plavix, aspirin, and nifedipine. She was discharged home on the day after sympathectomy.

At 2.5 months after the sympathectomy had been performed, and after the necrosis had demarcated, the patient underwent partial amputation of the ring finger through the distal interphalangeal joint and debridement of the distal pulps of the long and index finger (Fig. 4). She later had a revision amputation of the ring finger at the level of the

Fig. 4. Clinical photograph of the hand after partial amputation of the ring finger through the distal interphalangeal joint (DIP)

middle phalanx 3 months after her initial amputation. At final follow-up, after 10 months from the sympathectomy, the patient was doing well, had well-healed wounds, and still had some dysesthesias in her long and index fingers, but was stable to be discharged from our care.

Discussion

Promethazine is a commonly used medication to treat nausea and motion sickness, and it possesses antihistamine and sedative properties. Deep intramuscular injection into a large muscle is the preferred parenteral route of administration; however, severe tissue damage can occur regardless of the route of administration. Inadvertent intra-arterial or subcutaneous administration results in severe complications that require both medical and often surgical intervention.

There is no proven successful treatment for unintentional intra-arterial injection or perivascular extravasation. Treatment concepts in the acute phase include vasodilation by local anesthetic infiltration, intra-arterial vasodilators or sympathetic blockade (i.e., stellate ganglion), reduction of swelling through limb elevation, and anticoagulation (e.g., heparinization) [2, 6]. Other treatment options that have been suggested include high-dose steroids, hyperbaric oxygen therapy, and nitropaste (or other topical vasodilators) [6, 10]. In cases of inadvertent arterial injection, it has been recommended to leave the arterial line in place for confirmation of placement and possible direct intra-arterial delivery of vasodilators. Confirming intra-arterial injection as opposed to intravenous extravasation may also help predict local versus distal tissue necrosis. Prescription medications such as calcium channel blockers, papaverine, thorazine, and thromboxane inhibitors can also be used to manage arterial vasospasm. In the setting of acute thrombosis, thrombolytics can be considered.

Despite medical treatment, this complication often requires surgical management. To our knowledge, this is the first report of performing surgical peripheral sympathectomy to treat digital necrosis related to parenteral administration of promethazine. The long-term success of peripheral sympathectomy for digital vasospasm secondary to an autoimmune disease has been recently published [4]. And in general, patients with vascular damage and vasospasm do not respond well to medical therapy [4]. Thus, given the clear periadventitial scarring, thrombosis, and tissue damage seen in our patient at the time of surgery, we propose that surgical peripheral sympathectomy may lead to similar long-term improvement in tissue perfusion and pain relief in patients who have adverse events secondary to parenteral administration of promethazine. Despite all of these treatment measures, necrosis often occurs following extravasation or inadvertent arterial injection of promethazine. One should allow adequate time for the zone of necrosis to be defined before debridement or amputation. Hand therapy and rehabilitation should be considered in appropriate individuals as soon as tolerable [2].

Multiple reports have been submitted to the Institute for Safe Medication Practices, United States Pharmacopeia, and

the Pennsylvania Patient Safety Reporting Systems. Articles have been published in peer-reviewed journals warning clinicians of the potential morbidity associated with parenteral promethazine administration [1–3, 6–8]. It would seem that patient harm as a result of parenteral administration of promethazine is more common than most expect. However, despite these reports, many clinicians continue to prescribe the medication intravenously.

In summary, morbidity associated with parenteral administration of promethazine is more prevalent than anticipated. Given the lack of successful treatment options for intra-arterial or perivascular extravasation, an increase in medical malpractice awards, and the numerous therapeutic alternatives to promethazine, we question whether the drug should be administered intravenously or used at all. However, if this unfortunate complication occurs, peripheral sympathectomy can improve tissue perfusion and improve pain in these patients.

Disclosures Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Each author certifies that his or her institution has approved the reporting of this case, and that all investigations were conducted in conformity with ethical principles of research.

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