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Reversal of Digital Ischemia with Phentolamine After Accidental Epinephrine Injection

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Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 26-year-old
Final Diagnosis: Digital ischemia secondary to accidental epinephrine injection
Symptoms: Pain
Medication: —
Clinical Procedure: Local injection of phentolamine to reverse ischemia
Specialty: Plastic Surgery

Objective: Management of emergency care

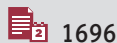
Background: Accidental finger-stick injuries have been reported with epinephrine autoinjectors, such as EpiPen and EpiPen Jr, and can result in necrosis and digital ischemia. However, long-term adverse effects are very rare. The treatment for accidental finger-stick injuries is controversial and includes intra-arterial injections of vasodilating agents, topical vasodilators, and supportive management as needed.

Case Report: Here, we report a case of a 26-year-old pharmacist who injected herself accidentally with an EpiPen on the tip of her index finger. Warm water and nitroglycerine gel did not alleviate her symptoms. After three hours, phentolamine was injected around the necrotic area, and the skin normalized.

Conclusions: All health professionals should be trained in how to handle epinephrine autoinjectors safely. Phentolamine may be efficacious in treating accidental finger-stick injuries from epinephrine autoinjectors.

MeSH Keywords: Accidental Injection • Autoinjector • Digital ischemia • EpiPen

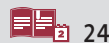
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Background

Epinephrine is the primary drug used in the management of severe anaphylaxis. For patients with serious allergies, it is crucial to be able to deliver epinephrine in a fast and efficient way, such as with an autoinjector [1]. The use of epinephrine autoinjectors has increased dramatically over the last two decades. Since 1980, severe anaphylaxis has been treated using epinephrine autoinjector devices, including EpiPen Jr[®] and EpiPen[®]. These enable a patient experiencing an acute allergic reaction to inject epinephrine quickly, which helps to reverse airway constriction, peripheral vasodilation, myocardial depression, and edema.

The majority of anaphylactic reactions are not treated with epinephrine despite the life-saving advantages of using epinephrine autoinjectors (EAI). The use of EAI is low owing to concerns about safety and lack of availability [2]. Potential injuries and inappropriate use remain concerns for both patients and physicians [3], including accidental injections, the use of expired EAI, laceration injuries, and cardiovascular complications. The true incidence of accidental EAI injections is unknown, but has been reported to be increasing [4]. In therapeutic doses, epinephrine can result in adverse complications, such as dizziness, anxiety, headache, restlessness, tremor, pallor, numbness, and palpitations. Extreme adverse consequences include pulmonary edema, ventricular arrhythmias, and hypertensive crisis [5]. The pharmacological impact of epinephrine might be detrimental in patients with heart disease because of elevated vascular resistance, contraction force, and heart rate, as well as vasoconstriction. There have been reports of finger necrosis after accidental low-dose (1: 100,000) epinephrine injection [6]. Myocardial infarction has also been reported from injected epinephrine [7].

Here, we report a case of a pharmacist who accidentally injected epinephrine into her index finger while handling an autoinjector. We also present relevant findings from the literature.

Case Report

A 26-year-old female pharmacist was brought to the hospital's Emergency Department (ED). She was a relatively new pharmacist, with 10 months of experience, and had received only general training and orientation with no training specific to injectors. She presented to the ED with pain in the right index finger after accidentally injecting herself with an epinephrine pen. The patient had injected the whole EpiPen, containing 0.3 mg of 1: 1000 epinephrine, into the bulb of the index finger (distal digit) at 9: 15 am. She presented to the ED around 9: 30 am, registered herself, and then left the ED. The patient was called back at 10: 30 am (Figure 1).

She was transferred immediately to the procedure room, where she was seen by the reporting doctor. She appeared to be well and reported no pain or other symptoms but did have a small needle puncture wound on the tip of the index finger. She reported no tachycardia, chest pain, shortness of breath, headache, or vomiting.

On examination, she had normal vitals. Her chest was clear to auscultation. The cardiovascular exam was normal, with a normal pulse rate, radial pulse, and abdominal exam. An examination of the central nervous system was conducted, with no abnormal findings. Her right index finger was pale, with an obvious needle entry point at the index bulb, which was black. The capillary refill time was 4 seconds in that finger only, while less than a second in her other fingers. She was not in pain, as confirmed using a numeric pain scale.



Figure 1. (A) Before starting the management, the right index finger was pale with a darkened puncture wound at the injection site. (B) Twenty minutes after the incident, the right index finger was still pale with a visible puncture wound at the injection point.



Figure 2. After immersion in water, the puncture wound at the tip of the right index finger had faded slightly.



Figure 3. After applying nitroglycerin, there was no further improvement.

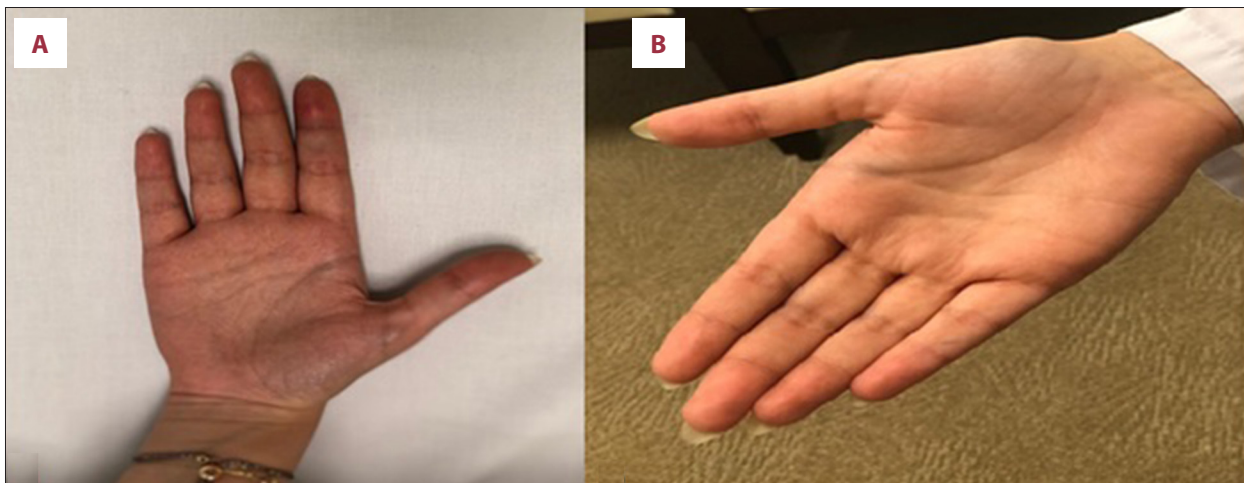


Figure 4. (A) Upon discharge, 6 hours after the incident, the right index finger had no pallor and slight hyperemia. (B) One month later, the right index finger appeared normal.

The patient was asked to hold her finger in a downwards position and submerge it in warm water for 20 minutes (Figure 2). On reassessment, there was no improvement in the finger pallor or the black puncture point. The only available formulation of nitroglycerin at that time was a mixture of lidocaine and nitroglycerine gel. So, lidocaine gel 2% with 0.4 mg nitroglycerin was applied on her finger, which was then wrapped with a Tegaderm transparent film dressing to hold it in place. This was done twice every 20 minutes, but no difference was reported in the pallor or the small necrotic part on the finger (Figure 3).

Later, phentolamine was delivered by the pharmacy as it took some time to prepare. Numbness and coldness had developed in the digit, which was treated with half a milligram of phentolamine around the dark area on the index finger. There was

an immediate change, and the skin color became pinkish. After 25 minutes, the skin was almost normalized. The patient had a normal finger during a follow-up visit in the plastic surgery outpatient clinic (Figure 4).

Discussion

The binding of epinephrine occurs via the blood vessels' α -adrenergic receptors, acting as an α - and β -adrenergic agonist, which causes a rise in vasoconstriction and vascular resistance. Often used for local vasoconstriction, an intramuscular or subcutaneous injection might delay absorption even though the epinephrine plasma half-life is approximately two to three minutes. Therefore, the effects of epinephrine might

be longer than its half-life [8]. Globally, the accidental injection rate of epinephrine has risen because of the increased use of autoinjectors, and has been found to occur once for every 50,000 EpiPen® units sold [9]. The EpiPen® trainer was self-injected by about 16% of doctors who read the EpiPen® device instructions and injected it into their thumbs [7]. This increases the risk of painful necrosis due to extreme local vasoconstriction, even though no case of digital loss has been recorded [7]. Immersion in warm water, topical nitroglycerin application, and nerve blockade are often administered. Ainsworth et al. [10] showed improvement and recovery using these methods, even though they did not help in our case. The subcutaneous injection of terbutaline has also been reported to reverse vasospasm.

Terbutaline is a selective β_2 agonist, which causes vasodilation with an increase in β_2 receptors in the vasculature. Pharmacologically, terbutaline can enable increased blood flow, reduce tissue ischemia, and reverse β_2 -mediated vasoconstriction in the peripheral vasculature, which makes this mechanism a likely option to manage vasopressor extravasation [11]. Likewise, terbutaline is considered as a better alternative to topical nitroglycerin for intense vasoconstriction reversal throughout extravasation because of its β_2 stimulation, leading to vasodilation [12]. Furthermore, it can be administered directly and locally into the extravasation site [13]. Terbutaline also appears to be more efficacious than nitroglycerin, which in one case took up to 1 month of sustained treatment to resolve symptoms. When the topical nitroglycerin failed, terbutaline alleviated the patient's symptoms, suggesting its effectiveness in auto-injection cases [11]. However, in this patient, phentolamine was used over terbutaline because of its availability in the hospital pharmacy.

The duration of anesthesia latency, in the presence of epinephrine, is minimal, suggesting that anesthetic solution should not be injected in adult patients. Furthermore, a minimal dose of local anesthetic is conceptually valid for solutions with epinephrine and without [14]. From multiple case studies and case series, few long-term adverse effects of accidental epinephrine digital injection have been reported [15,16]. This is accepted by the plastic surgery community and identified in the emergency medicine literature [17,18]. Paresthesia is the most commonly reported adverse reaction to digital epinephrine, and this generally resolves in less than six months [19].

In 1957, phentolamine was introduced as an α -blocker and catecholamine vasoconstriction protective agent [20], and has been identified as the reversal agent of choice because of its consistency in experimental studies. It is reported that epinephrine vasoconstriction in the human finger has been completely reversed by injection of 1 mg of phentolamine in 1 cm³ of saline for an average of 1 h and 25 minutes [20].

Even with conservative management, epinephrine-induced digital ischemia has low long-term morbidity. Subcutaneous injection of phentolamine or terbutaline is included in traditional treatment options. These reversal agents are considered good alternatives if necrosis, with symptoms showing no timely resolution, has been identified [19,21]. Two topical vasodilators, topical calcium channel blockers and topical nitroglycerin, are considered alternative, less invasive treatment methods. These methods have been minimally used but have been shown to be efficacious.

Indirectly, accidental EAI injection could be fatal if an anaphylactic attack occurs and cannot be treated because the entire dose has been used [22]. The occurrence rate of accidental injections is 10% when administering an EAI to a patient. Therefore, delayed epinephrine administration might occur. One child died when a caregiver auto-injected with an EAI [23]. However, as yet, there is little evidence that gives insight into the significance and prevalence of the lost-dose risk [23].

All health professionals should receive formal training regarding prescribing and issuing EAIs. EAIs are only to be prescribed after the patient has been informed of the likely effects of incorrect administration, and pharmacists and physicians should be able to confidently give appropriate advice to patients. In the future, phentolamine should be introduced as a treatment for accidental epinephrine injection. The present case study also emphasizes the need for all healthcare professionals to be able to rapidly access information, and technologies should be made available for accessing medical databases [24].

EAIs are efficacious in treating anaphylaxis. However, the occurrence of accidental digital epinephrine injection is not rare. Different treatment methods have been described in several case reports, which vary from conservative management to local infiltration with α -antagonists. However, there is still no standard protocol for epinephrine-induced digital ischemia. Therefore, it is recommended that conservative measures are tried initially. An injection of phentolamine is advisable if the digital ischemia does not respond to this initial treatment. If the patient suffers from peripheral vascular disease, the use of phentolamine may be advisable from the outset.

Conclusions

This case highlighted the use of phentolamine as treatment after the accidental injection of epinephrine with an autoinjector. The advantages of local infiltration with phentolamine and outcomes until complete perfusion recovery were discussed, including reduction in the duration of the symptoms as a result of local treatment with phentolamine, which helped to lower vasoconstriction and allow the return and recovery of capillary

refill. This case also demonstrates the need for all healthcare professionals and patients to be educated in the appropriate management and administration of EAI to reduce the occurrence of accidental injections.

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Conflict of interest

None.

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