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Views and Practice

Extravasation injury due to intravenous promethazine: a reminder to healthcare professionals

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A 22-year-old gentleman sustained a hornet sting on his right hand and subsequently developed generalised urticaria over his chest, trunk and back within 30 minutes. His vital signs were normal and he had no other symptoms and signs of anaphylaxis. He received a bolus of 1 mL of 25 mg/mL of promethazine (total 25 mg) which was injected into the dorsal vein of his left hand over one minute. Within six hours, the majority of his urticaria resolved.

However, 48 hours after the promethazine injection, he developed painful swelling of his left upper limb. On physical examination, his left forearm was oedematous with scattered reticulate purpuric patches associated with two discrete bullae (Figure 1). Clinically, the left brachial and left radial pulses were clearly palpable and capillary refill time over the tips of his fingers were less than two seconds. The provisional clinical diagnoses were (1) extravasation injury and (2) thrombo-occlusion phenomenon.

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Arterial and venous duplex scans were performed which were normal. A thrombophilia screen that included protein C, protein S, factor V and antithrombin III was performed and all were within normal limits. A skin biopsy showed extensive necrolysis predominantly affecting the basal zone of the epidermis. There was also cell-poor picture and subepidermal blistering (Figure 2a). The superficial dermis showed extravasated red blood cells with relatively mild chronic inflammatory cell infiltrate which included fairly prominent eosinophils (Figure 2b). The histological features were consistent with extravasation injury,[1] caused by promethazine. He was treated with arm elevation, saline compression and topical corticosteroids. After six weeks of topical treatment, there was complete resolution of the bullae leaving residual postinflammatory hyperpigmentation over the affected arm.

Promethazine is a phenothiazine derivative that has anti-histamine, anti-muscarinic sedative, anti-motion sickness, antiemetic and anti-cholinergic effects. It was first approved by the United States Food and Drug Administration (FDA) in 1956. The main indications for promethazine include the following: (1) mitigation of allergic reactions, (2) as an adjunct to epinephrine and other standard measures in anaphylaxis. Other indications include sedation, relief of apprehension, active control of motion sickness and prevention and control of nausea and vomiting associated with certain types of anaesthesia and surgery.[2] Its administration

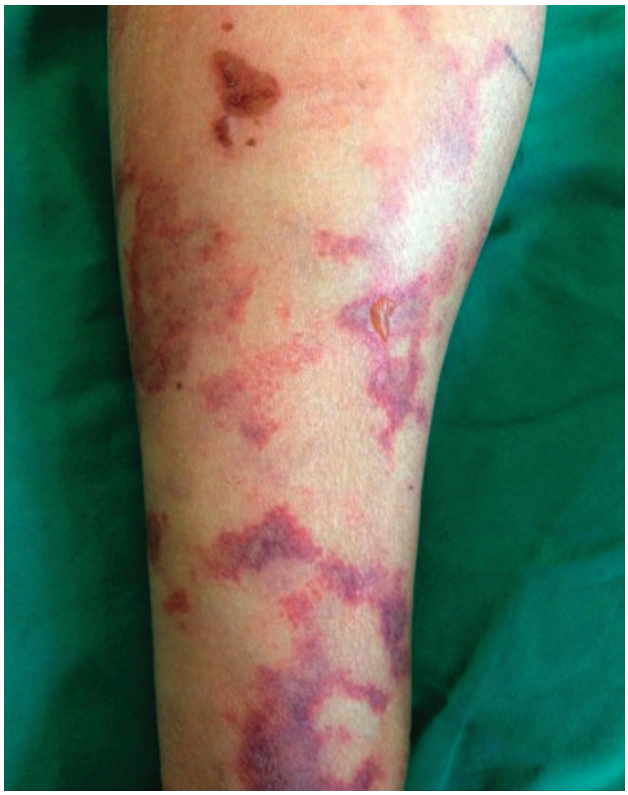

Figure 1. Oedematous left forearm with scattered reticulate purpuric patches with two discrete bullae.

includes intravenous, intramuscular and oral routes.

Promethazine has been used since 1956 with a good safety profile, clinicians are comfortable with promethazine use.[3] However, promethazine use is not without risks: it is a known vesicant which is highly caustic to the intima of blood vessels and surrounding tissue. Formulated with phenol, promethazine has a pH between 4 and 5.5.

Although deep intramuscular injection into a large muscle is the preferred parenteral route of administration, product labelling states promethazine may be given intravenously, which is how it is administered in most hospitals and healthcare facilities.[4]

Promethazine can cause tissue damage, regardless of the route of parenteral administration, although intravenous, and inadvertent intra-arterial or subcutaneous administration causes more severe complications.[2] The FDA is aware of the perils

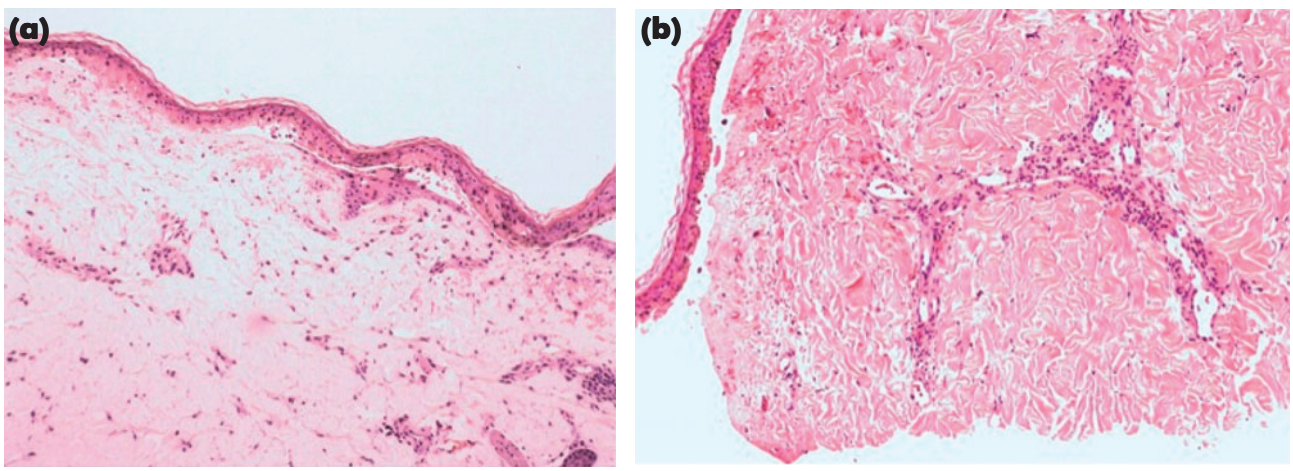

Figure 2. (a) Extensive necrolysis predominantly affecting the basal zone of the epidermis. There was also cell poor, subepidermal blistering (H&E x100). (b) Extravasated red blood cells in superficial dermis with relatively mild chronic inflammatory cell infiltrate which included fairly prominent eosinophils (H&E x100).

of perivascular extravasation and inadvertent intra-arterial administration causing severe tissue injury that are associated with intravenous administration of promethazine. The FDA reviewed the published literature and post-marketing adverse event reports submitted to FDA's Adverse Event Reporting System from 1969 to 2009 and identified cases of gangrene requiring amputation associated with intravenous administration of promethazine. Other complications include burning, erythema, pain, swelling, severe vasospasm, thrombophlebitis, venous thrombosis, nerve damage, paralysis and abscess.[5]

In light of the above, the FDA in September 2009 mandated manufacturers of promethazine to include a boxed warning regarding the injectable form of the drug. The warning highlights the risk of serious tissue injury when the drug is administered incorrectly. The following points are highlighted in the FDA guidelines: [5]

- Intravenous administration of promethazine can cause severe tissue injury, including gangrene, requiring fasciotomy, skin graft and/or amputation
- Severe tissue injury can occur from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration
- Deep intramuscular injection is the preferred way to administer promethazine injection
- Intra-arterial and subcutaneous administration of promethazine are contraindicated
- If intravenous administration of promethazine is required, the maximum recommended concentration is 25 mg per mL and the maximum recommended rate of administration is 25 mg per minute through the tubing of an intravenous infusion set known to be functioning properly
- Be alert for symptoms and signs of potential tissue injury including burning or pain at the site of injection, phlebitis, swelling and blistering
- Injections should be stopped immediately if a patient complains of pain during injection
- Inform patients that side effects may occur immediately while receiving the injection or may develop hours to days after an injection

In conclusion, promethazine is a useful medication that can effectively treat and mitigate allergic reactions. Use of promethazine can cause severe tissue damage, regardless of the route of parenteral administration. However, physicians need to be cognisant of the risk of extravasation injury that intravenous promethazine can cause and follow FDA's recommendations whenever promethazine is adminstered.

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