Hyaluronidase for Skin Necrosis Induced by Amiodarone

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PRACTICE **POINTS**

- Intravenous amiodarone administered peripherally can induce skin extravasation, leading to necrosis.
- Dermatologists should be aware that early intervention with intradermal hyaluronidase may reduce the severity of tissue damage caused by amiodarone-induced skin necrosis.

To the Editor:

Amiodarone is an oral or intravenous (IV) drug commonly used to treat supraventricular and ventricular arrhythmia as well as atrial fibrillation.[1] Adverse drug reactions associated with the use of amiodarone include pulmonary, gastrointestinal, thyroid, ocular, neurologic, and cutaneous reactions.[1] Long-term use of amiodarone—typically more than 4 months—can lead to slate-gray skin discoloration and photosensitivity, both of which can be reversed with drug withdrawal.[2,3] Phlebitis also has been described in less than 3% of patients who receive peripheral IV administration of amiodarone.[4]

Amiodarone-induced skin necrosis due to extravasation is a rare complication of this antiarrhythmic medication, with only 3 reported cases in the literature according to a PubMed search of articles indexed for MEDLINE using the search terms *amiodarone* and *skin* and (*necrosis* or *ischemia* or *extravasation* or *reaction*).[5–7] Although hyaluronidase is a known therapy for extravasation of fluids, including parenteral nutrition and chemotherapy, its use for the treatment of extravasation from amiodarone is not well documented.[6] We report a case of skin necrosis of the left dorsal forearm and the left dorsal and ventral hand following infusion of amiodarone through a peripheral IV line, which was treated with injections of hyaluronidase.

A 77-year-old man was admitted to the emergency department for sepsis secondary to cholangitis in the setting of an obstructive gallbladder stone. His medical history was notable for multivessel coronary artery disease and atrial flutter treated with ablation. One day after admission, endoscopic retrograde cholangiopancreatography was attempted and aborted due to atrial fibrillation with rapid ventricular response. A second endoscopic retrograde cholangiopancreatography attempt was made 4 days later, during which the patient underwent cardiac arrest. During this event, amiodarone was administered in a 200-mL solution (1.8 mg/mL) in 5% dextrose through a peripheral IV line in the left forearm. The patient was stabilized and transferred to the intensive care unit.

Twenty-four hours after amiodarone administration, erythema was noted on the left dorsal forearm. Within hours, the digits of the hand became a dark, dusky color, which spread to involve the forearm. Surgical debridement was not deemed necessary; the left arm was elevated, and warm compresses were applied regularly. Within the next week, the skin of the left hand and dorsal forearm had progressively worsened and took on a well-demarcated, dusky blue hue surrounded by an erythematous border involving the proximal forearm and upper arm (Figure 1A). The skin was fragile and had overlying bullae (Figure 1B).

Hyaluronidase (1000 U) was injected into the surrounding areas of erythema, which resolved from the left

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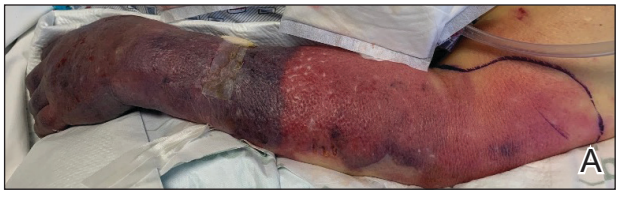
proximal forearm to the elbow within 2 days after injection (Figure 2). The dusky violaceous patches were persistent, and the necrotic bullae were unchanged. Hyaluronidase (1000 U) was injected into necrotic skin of the left dorsal forearm and dorsal and ventral hand. No improvement was noted on subsequent evaluations of this area. While still an inpatient, he received wound care and twice-daily Doppler ultrasounds in the areas of necrosis. The patient lost sensation in the left hand with increased soft tissue necrosis and developed an eschar on the left dorsal forearm. Due to the progressive loss of function and necrosis, a partial forearm amputation was performed that healed well, and the patient experienced improvement in range of motion of the left upper extremity.

Well-known adverse reactions of amiodarone treatment include pulmonary fibrosis, hepatic dysfunction, hypothyroidism and hyperthyroidism, peripheral neuropathy, and corneal deposits.[1] Cutaneous adverse reactions include photosensitivity (phototoxic and photoallergic reactions), hyperpigmentation, pseudoporphyria, and linear IgA bullous dermatosis. Less commonly, it also can cause urticaria, pruritus, erythema nodosum, purpura, and toxic epidermal necrolysis.[3] Amiodarone-induced skin necrosis is rare, first described by Russell and Saltissi[5] in 2006 in a 60-year-old man who developed dark discoloration and edema of the forearm 24 hours after initiation of an amiodarone peripheral IV. The patient was treated with hot or cold packs and steroid cream per the pharmaceutical company's recommendations; however, patient outcomes were not discussed.[5] A 77-year-old man who received subcutaneous amiodarone due to misplaced vascular access developed edema and bullae of the forearm followed by tissue necrosis, resulting in notably reduced mobility.[6] Fox et al[7] described a 60-year-old man who developed atrial fibrillation after emergent spinal fusion and laminectomy. He received intradermal hyaluronidase administration within 24 hours of developing



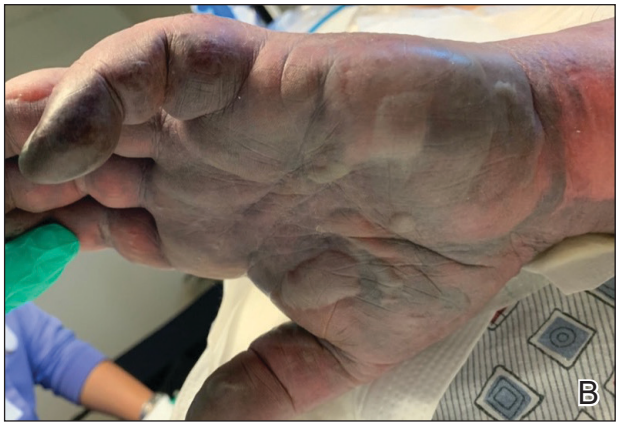
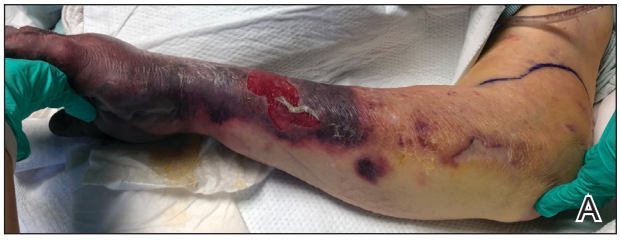


FIGURE 1. A, Erythema on the dorsal aspect of the left hand and forearm with a well-demarcated, dusky blue hue, surrounded by an erythematous border on the proximal forearm and upper arm. B, Bullae overlying darkened skin were present on the left palm.



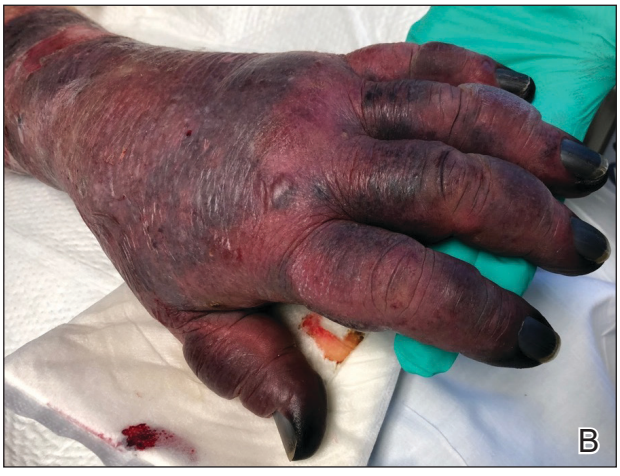


FIGURE 2. A, Resolution of erythema on the left proximal forearm to the elbow after the first administration of hyaluronidase. B, Left dorsal aspect of the hand. C, Persistence of dusky violaceous patches and necrotic bullae on the left palm.

severe pain from extravasation induced by amiodarone with no adverse outcomes and full recovery.[7]

There are numerous properties of amiodarone that may have resulted in the skin necrosis seen in these cases. The acidic pH (3.5–4.5) of amiodarone can contribute to coagulative necrosis, cellular desiccation, eschar formation, and edema.[8] It also can contain additives such as polysorbate and benzyl alcohol, which may contribute to the drug's vesicant properties.[9]

Current recommendations for IV administration of amiodarone include delivery through a central vein with high concentrations (>2 mg/mL) because peripheral infusion is slower and may cause phlebitis.[4] In-line filters also may be a potential method of preventing phlebitis with peripheral IV administration of amiodarone.[10] Extravasation of amiodarone can be treated nonpharmacologically with limb elevation and warm compresses, as these methods may promote vasodilation and enhance drug removal.[5-7] However, when extravasation leads to progressive erythema and skin necrosis or is refractory to these therapies, intradermal injection of hyaluronidase should be considered. Hyaluronidase mediates the degradation of hyaluronic acid in the extracellular matrix, allowing for increased permeability of injected fluids into tissues and diluting the concentration of toxins at the site of exposure.[9,11] It has been used to treat extravasation of fluids such as parenteral nutrition, electrolyte infusion, antibiotics, aminophylline, mannitol, and chemotherapy.[11] Although hyaluronidase has been recognized as therapeutic for extravasation, there is no established consistent dosing or proper technique. In the setting of infiltration of chemotherapy, doses of hyaluronidase ranging from 150 to 1500 U/mL can be subcutaneously or intradermally injected into the site within 1 hour of extravasation. Side effects of using hyaluronidase are rare, including local pruritus, allergic reactions, urticaria, and angioedema.[12]

The patient described by Fox et al[7] who fully recovered from amiodarone extravasation after hyaluronidase injections likely benefited from quick intervention, as he received amiodarone within 24 hours of the care team identifying initial erythema. Although our patient did have improvement of the areas of erythema on the forearm, evidence of skin and subcutaneous tissue necrosis on the left hand and proximal forearm was already apparent and not reversible, most likely caused by late intervention of intradermal hyaluronidase almost a week after the extravasation event. It is important to identify amiodarone as the source of extravasation and administer intradermal hyaluronidase in a timely fashion for extravasation refractory to conventional measurements to prevent progression to severe tissue damage.

Our case draws attention to the risk for skin necrosis with peripheral IV administration of amiodarone. Interventions include limb elevation, warm compresses, and consideration of intradermal hyaluronidase within 24 hours of extravasation, as this may reduce the severity of subsequent tissue damage with minimal side effects.

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