



BRIEF  
ANSWERS  
TO SPECIFIC  
CLINICAL  
QUESTIONS

## 1-MINUTE CONSULT

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# Q: What is the optimal approach to infiltration and extravasation of nonchemotherapy medications?

**A:** The immediate response to leakage of intravenous (IV) medications is warm or cold compression and assessment of severity. If the severity is grade 3 or above,<sup>1</sup> an antidote is needed and must be identified quickly. The antidote depends on the type of medication that has leaked.

In general, hyaluronidase is the antidote of choice for nonvesicant agents, but other agents include topical nitroglycerin, phentolamine, terbutaline, and sodium thiosulfate. These agents work by vasodilating to clear the drug from the area and neutralizing the harmful irritants.

## ■ IMPORTANT DISTINCTIONS: TERMINOLOGY

An review of terminology is helpful when discussing leakage of IV fluids.

A **vesicant** is an agent capable of causing tissue damage when escaped from the intended vascular pathway into surrounding tissue.

An **irritant or nonvesicant** is an agent that causes discomfort including, aching, tightness, and phlebitis with or without inflammation, but does not typically cause tissue necrosis.

**Infiltration** is leakage of a nonvesicant solution into the surrounding tissue. It is a relatively common occurrence and can cause redness, swelling, and pain or discomfort but does not cause tissue necrosis.

**Extravasation** is leakage of vesicant fluid out of a blood vessel into surrounding tissue. It can cause more damage than infiltration of nonvesicant solutions and can lead to blistering, tissue ischemia, and necrosis. In extreme cases, surgical debridement, skin-grafting, or even amputation may be required.

doi:10.3949/ccjm.90a.22029

In this article, we will use the terms extravasation and extravasated for any IV infusion-related leakage.

## ■ THE PROBLEM

The frequency of extravasation in adults is between 0.1% and 6%.<sup>2</sup> Some suggest the incidence is decreasing thanks to improved infusion procedure, early recognition of drug leakage, and training.<sup>2</sup>

The consequences of fluid leakage from a vessel into surrounding tissue vary depending on the agent being dispensed. Awareness of these agents and their potential consequences will enhance the likelihood of prompt recognition and treatment.

## ■ IMMEDIATE INTERVENTIONS

The following immediate interventions are recommended to prevent complications:

- Stop administration of fluid
- Disconnect the IV tubing, but leave the catheter or needle in place to facilitate aspiration of fluid from the extravasation site and, if indicated, administration of an antidote
- Do not flush the line
- Remove the catheter or needle if an antidote will not be administered into the extravasation site
- If an antidote is indicated, inject it through the catheter to ensure delivery to the extravasation site, then remove the catheter
- Elevate the site and apply warm or cold compresses.

## Thermal compression and massage

Thermal compression improves patient outcomes.<sup>3</sup> Cooling with ice packs aids in vasoconstriction, theoretically restricts spread of the drug, and decreases

**TABLE 1**  
**Grading the severity of extravasation damage**

| Grade | Presentation   | Treatment   |
|-------|--|---|
| 1     | Minimal swelling, pain at infusion site  | Stop infusion<br>Remove cannula and tapes<br>Elevate  |
| 2     | Pain at infusion site, mild swelling, no skin-blanching, minimal redness, normal capillary refill time   | Stop infusion<br>Remove cannula and tapes<br>Elevate  |
| 3     | Pain at infusion site, swelling, skin-blanching with or without redness at the infusion site, sluggish capillary refill time, normal or decreased perfusion, hard to flush cannula   | Stop infusion<br>Leave cannula until reviewed by a doctor<br>Photograph injury if this will not delay treatment<br>Provider to commence irrigation procedure within 1 hour of extravasation by irrigating affected area using saline or appropriate antidote<br>Apply nonocclusive dressing as advised<br>Elevate limb<br>Consider plastic surgery team consult<br>Nursing staff to continue to observe the site hourly for the first 24 hours to monitor for adverse effects<br>Provider should review the site 1–2 hours after antidote to assess effectiveness, and reviewed again in 24 hours |
| 4     | Pain at infusion site, marked swelling, skin-blanching, coolness, reduced capillary refill time, decreased perfusion, with or without arterial occlusion, with or without blistering | Stop infusion<br>Leave cannula until reviewed by clinician<br>Photograph injury if this will not delay treatment<br>Commence irrigation procedure within 1 hour of extravasation by irrigating affected area using saline or appropriate antidote<br>Apply nonocclusive dressing as advised<br>Elevate limb<br>Refer to plastic surgery team<br>Nursing staff to continue to observe the site hourly for the first 24 hours to monitor for adverse effects<br>Review the site 1–2 hours after antidote to assess effectiveness, and review again in 24 hours                                      |

Based on information in references 5 and 6.

pain and inflammation in the area. Warming the affected area with dry heat promotes vasodilation and increases blood flow, enhancing dispersion of the vesicant agent and decreasing accumulation of the drug in the localized tissue.

The standard of care and recommended application schedule for both warming and cooling is 15 to 20 minutes 4 times daily for 24 to 48 hours.<sup>2</sup> Some guidelines suggest up to 6 times daily for 1 or more days.<sup>2</sup>

Physical massage may aid in the dispersal of extravasated drugs. To monitor and document the leakage, a surgical felt pen is used to gently draw an outline on the skin of the affected area.

## GAUGING THE SEVERITY, SELECTING AN ANTIDOTE

Many patients with extravasation experience erythema, edema, ulceration, stinging, burning, pain, tissue-sloughing, and even necrosis. A severity of grade 3 or greater, which requires an antidote, is characterized by pain, swelling, sluggish capillary refill time, normal or decreased perfusion, and other symptoms (Table 1).<sup>1,4–6</sup>

Treatment differs depending on the extravasated medication, and the selection process may be complex. In general, hyaluronidase is the antidote of choice for nonvesicant agents. Other antidotes include topical

**TABLE 2**  
**Current antidotes for intravenous extravasation**

| Antidote                             | Mechanism and use  | Preparation  | Administration   |
|--------------------------------------|--|--|--|
| Sodium thiosulfate <sup>5-7</sup>    | Neutralizes reactive species and reduces formation of hydroxyl radicals that can cause tissue injury             | From 25% sodium thiosulfate solution: mix 1.6 mL with 8.4 mL sterile water for injection                               | Use 2 mL of the prepared solution for each 1 mg of drug extravasated             |
|                                      | Used as first line for most vesicants  | From 10% sodium thiosulfate solution: mix 4 mL with 6 mL sterile water for injection                                   |  |
| Hyaluronidase <sup>7</sup>           | Hydrolyzes hyaluronic acid in connective tissue, possibly leading to dilution and diffusion of extravasated drug | To obtain a 15-unit/mL concentration, mix 0.1 mL (of 150 units/mL) with 0.9 mL of 0.9% sodium chloride in 1-mL syringe | Ideally administer within 1 hour of the event                                    |
|                                      | Used as first line for most vesicants  | Usually dosed as 15 to 25 units intradermally over 5 injections  |  |
| Phentolamine <sup>5,7</sup>          | Alpha-adrenergic antagonist that promotes vasodilation and capillary blood flow                                  | 5 to 10 mg in 10 to 20 mL of 0.9% sodium chloride  | Administer within 12 to 13 hours of the injury                                   |
|                                      | Used as preferred agent for vasopressors   |  |  |
| Nitroglycerin topical <sup>5,7</sup> | Increases nitric oxide, promoting vasodilation   | 2% ointment: A half-inch of ointment equals 7.5 mg of nitroglycerin  | 1-inch strip applied to site of ischemia; can re-dose every 8 hours as necessary |
|                                      | Used for vasopressors (alternative to phentolamine)  | 5-mg/day transdermal patch   | 1 patch daily  |
| Terbutaline <sup>5,7</sup>           | Alpha-adrenergic agonist that promotes vasodilation and capillary blood flow                                     | 1 mg in 10 mL of 0.9% sodium chloride  | Inject locally across symptomatic sites  |
|                                      | Used for vasopressors (alternative to phentolamine)  |  |  |

nitroglycerin, phentolamine, terbutaline, and sodium thiosulfate. Their vasodilating effects clear the drug from the affected area and neutralize harmful irritants that cause discomfort (aching, tightness, and phlebitis with or without inflammation) but typically not tissue necrosis. The treatment varies depending on the medication involved and the grade of severity (Tables 2 and 3).<sup>1-8</sup>

## ■ CONTRAST MEDIA EXTRAVASATION

Extravasation of IV-administered iodine-based and gadolinium-based contrast media can cause serious tissue damage, including necrosis. While the incidence of contrast media extravasation is relatively low (between 0.1% and 0.9%),<sup>9-11</sup> factors associated

with increased risk of contrast extravasation include use of iodine-based contrast (as opposed to gadolinium contrast), use of automatic power injectors, high injection rates, patient-related factors (older age, female sex, cachexia, IV drug use, inpatient status), venous access site (dorsum of hand), and small-gauge needles (less than 22-gauge).<sup>9,12</sup> Use of high-osmolar and high-viscosity contrast media increases the risk of extravasation. Prewarming the contrast agent to 37°C (98.6°F) lowers the viscosity and, in turn, the probability of extravasation.<sup>9</sup>

The clinical presentation of contrast extravasation resembles that of other vesicant drug extravasations and can include local pain, tenderness, swelling, redness, itching, and skin tightness. In more severe

**TABLE 3**  
**Antidotes for nonchemotherapy drug extravasation**

| Extravasated drug                         | Classification: vesicant or irritant           | Immediate topical treatment     | Antidote  |
|---|--|---------------------------------|---|
| Acyclovir <sup>2,5-7</sup>                | Irritant or vesicant; alkaline agent (pH 11)   | Cooling                         | Hyaluronidase   |
| Aminophylline <sup>2,4</sup>              | Vesicant; alkaline agent (pH 8–10)             | Warming                         | Hyaluronidase   |
| Amiodarone <sup>1,6,8</sup>               | Vesicant; acidic agent (pH 3.5–4.5)            | Warming                         | Hyaluronidase   |
| Amphotericin B <sup>4</sup>               | Vesicant; acidic agent (pH 5–7)                | Cooling                         | Hyaluronidase; for liposomal, consider flushout instead                       |
| Ampicillin <sup>4</sup>                   | Vesicant; hyperosmolar agent                   | Warming                         | Hyaluronidase   |
| Calcium chloride 10% <sup>2,4</sup>       | Vesicant; hyperosmolar agent                   | Warming                         | Early-onset: hyaluronidase<br>Delayed-onset: sodium thiosulfate               |
| Dantrolene <sup>4</sup>                   | Vesicant; alkaline agent (pH 9.5–10.3)         | Warming                         | Hyaluronidase   |
| Dextrose 10%–50% <sup>4</sup>             | Vesicant; hyperosmolar agent                   | Warming                         | Hyaluronidase   |
| Dobutamine <sup>2,4</sup>                 | Vesicant; vasopressor                          | Warming                         | First-line: phentolamine<br>Second-line: terbutaline/topical nitroglycerin    |
| Dopamine <sup>2,4</sup>                   | Vesicant; vasopressor                          | Warming                         | First-line: phentolamine<br>Second-line: terbutaline/topical nitroglycerin    |
| Doxycycline <sup>4</sup>                  | Vesicant; acidic agent (pH 1.8–3.3)            | Warming                         | Hyaluronidase   |
| Epinephrine <sup>2,4</sup>                | Vesicant; vasopressor                          | Warming                         | First-line: phentolamine<br>Second-line: terbutaline/topical nitroglycerin    |
| Esmolol <sup>4</sup>                      | Vesicant; acidic agent (pH 4.5–6.5)            | Warming (no literature support) | Hyaluronidase   |
| Etomidate <sup>2,4</sup>                  | Irritant (rarely vesicant); hyperosmolar agent | Warming (no literature support) | Hyaluronidase   |
| Lorazepam <sup>4</sup>                    | Vesicant; hyperosmolar agent                   | Warming (no literature support) | Hyaluronidase   |
| Mannitol 20% <sup>4</sup>                 | Vesicant; hyperosmolar agent                   | Warming                         | Hyaluronidase   |
| Metronidazole <sup>4</sup>                | Vesicant; acidic agent (pH 5.5)                | Warming (no literature support) | Hyaluronidase   |
| Methylene blue <sup>4</sup>               | Vesicant; vasopressor                          | Warming (no literature support) | First-line: topical nitroglycerin<br>Second-line: phentolamine or terbutaline |
| Nafcillin <sup>4</sup>                    | Vesicant or irritant                           | Warming                         | Hyaluronidase   |
| Nitroglycerin <sup>2</sup>                | Vesicant; hyperosmolar agent                   | Warming or cooling              | Hyaluronidase   |
| Norepinephrine <sup>2,4</sup>             | Vesicant; vasopressor                          | Warming                         | First-line: phentolamine<br>Second-line: terbutaline/topical nitroglycerin    |
| Parenteral nutrition <sup>2,4</sup>       | Vesicant; hyperosmolar agent                   | Warming                         | Hyaluronidase, nitroglycerin  |
| Pentobarbital <sup>4</sup>                | Vesicant; alkaline agent (pH 9–10.5)           | Warming                         | Hyaluronidase   |
| Phenobarbital <sup>2,4</sup>              | Vesicant; hyperosmolar agent                   | Warming (no literature support) | Hyaluronidase   |
| Phenylephrine <sup>2,4</sup>              | Vesicant; vasopressor                          | Warming                         | First-line: phentolamine<br>Second-line: topical nitroglycerin                |
| Phenytoin and fosphenytoin <sup>2,4</sup> | Vesicant; alkaline agent (pH 10–12)            | Warming                         | Hyaluronidase or nitroglycerin  |
| Potassium chloride <sup>2,4</sup>         | Irritant; hyperosmolar agent                   | Warming                         | Hyaluronidase   |
| Potassium phosphate <sup>6</sup>          | Irritant; hyperosmolar agent                   | Cooling                         | Hyaluronidase   |
| Sodium bicarbonate 8.4% <sup>2,4</sup>    | Vesicant; hyperosmolar agent                   | Warming                         | Hyaluronidase   |
| Sodium chloride (> 3%) <sup>2,4</sup>     | Vesicant; hyperosmolar agent                   | Warming                         | Hyaluronidase   |
| Sodium phosphate <sup>4</sup>             | Vesicant; hyperosmolar agent                   | Warming                         | Hyaluronidase   |
| Penicillin <sup>4</sup>                   | Vesicant                                       | Warming (no literature support) | Hyaluronidase   |
| Valproate <sup>4</sup>                    | Vesicant                                       | Cooling                         | Hyaluronidase with washout  |
| Vancomycin <sup>4</sup>                   | Irritant or vesicant; acidic agent             | Warming (no literature support) | Hyaluronidase   |
| Vasopressin <sup>4</sup>                  | Vesicant; vasopressor                          | Warming                         | First-line: topical nitroglycerin<br>Second-line: phentolamine or terbutaline |

cases or with large-volume, high-osmolality contrast extravasation, skin-blistering, soft-tissue necrosis, or compartment syndrome can occur.

Treatment requires immediate discontinuation of the infusion, aspiration of contrast if possible, conservative measures such as limb elevation and cooling compresses, and injection of hyaluronic acid. There is no set threshold of extravasate volume at which surgical consultation is warranted. However, it has been suggested that plastic surgery consultation be requested when extravasation volume is greater than 100 to 150 mL.<sup>9,13</sup> Severe symptoms such as ulceration or necrosis may warrant surgical consultation regardless of extravasate volume.

## PREVENTION

Focusing on preventive measures will lower the risk

of extravasation, promote patient trust, and increase patient satisfaction.<sup>2</sup> Patient engagement is key to prevention. When infusing a vesicant, counsel the patient to immediately report changes in skin color, integrity or firmness, temperature, mobility, sensation, or pain.<sup>2</sup> The vein used for infusion should be a large, intact vessel with good blood flow, specifically a basilic, cephalic, or antebrachial vein. Avoid veins in the hands, dorsum of the foot, any joint space, or antecubital fossa area.<sup>2</sup> Always check for blood back-flow to ensure correct catheter positioning.<sup>2</sup> When possible, use of a central venous catheter helps limit drug extravasation.<sup>14</sup>

## DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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