Abby Tarpey, PharmD
School of Pharmacy and Health Professions, Creighton University, Omaha, NE

Shraddha Narechania, MD, FCCP
Assistant Professor, Department of Internal Medicine, Campbell University, Buies Creek, NC

Mark Malesker, PharmD, FCCP, FCCM, FASHP, BCPS
Professor of Pharmacy Practice and Medicine, Creighton University School of Medicine, Omaha, NE

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

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,[1] 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%.[2] Some suggest the incidence is decreasing thanks to improved infusion procedure, early recognition of drug leakage, and training.[2]

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.[3] Cooling with ice packs aids in vasocontriction, 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 Remove cannula and tapes Elevate
2	Pain at infusion site, mild swelling, no skin-blanching, minimal redness, normal capillary refill time	Stop infusion Remove cannula and tapes 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 Leave cannula until reviewed by a doctor Photograph injury if this will not delay treatment Provider to commence irrigation procedure within 1 hour of extravasation by irrigating affected area using saline or appropriate antidote Apply nonocclusive dressing as advised Elevate limb Consider plastic surgery team consult Nursing staff to continue to observe the site hourly for the first 24 hours to monitor for adverse effects 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 Leave cannula until reviewed by clinician Photograph injury if this will not delay treatment Commence irrigation procedure within 1 hour of extravasation by irrigating affected area using saline or appropriate antidote Apply nonocclusive dressing as advised Elevate limb Refer to plastic surgery team Nursing staff to continue to observe the site hourly for the first 24 hours to monitor for adverse effects 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.[2] Some guidelines suggest up to 6 times daily for 1 or more days.[2]

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**).[1,4–6]

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

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**).[1–8]

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%),[9–11] 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).[9,12] 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.[9]

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

cases or with large-volume, high-osmolarity 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.[9,13] 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.[2] 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.[2] 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.[2] Always check for blood backflow to ensure correct catheter positioning.[2] When possible, use of a central venous catheter helps limit drug extravasation.[14]

DISCLOSURES

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

REFERENCES

1. **The Royal Children's Hospital Melbourne.** Clinical guidelines (nursing). Extravasation injury management. https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Extravasation_Injury_Management/. Accessed April 11, 2023.
2. **Kim JT, Park JY, Lee HJ, Cheon YJ.** Guidelines for the management of extravasation. J Educ Eval Health Prof 2020; 17:21. doi:10.3352/jeehp.2020.17.21
3. **Roca-Sarsanedas J, Galimany-Masclans J, Regidor-Braojos AM, Falcó-Pegueroles A.** Topical treatment of tissue damage due to extravasation of iodinated contrast using thermal compresses. J Tissue Viability 2022; 31(1):135–141. doi:10.1016/j.jtv.2021.12.0063.
4. **Ong J, Van Gerpen R.** Recommendations for management of noncytotoxic vesicant extravasations. J Infus Nurs 2020; 43(6):319–343. doi:10.1097/NAN.0000000000000392
5. **University of Illinois, Chicago.** What are current recommendations for treatment of drug extravasation? https://dig.pharmacy.uic.edu/faqs/2021-2/february-2021-faqs/what-are-current-recommendations-for-treatment-of-drug-extravasation. Accessed April 11, 2023.
6. **Reynolds PM, MacLaren R, Mueller SW, Fish DN, Kiser TH.** Management of extravasation injuries: a focused evaluation of noncytotoxic medications. Pharmacotherapy 2014; 34(6):617–632. doi:10.1002/phar.1396
7. **Lau BC, Lee NH.** Acyclovir extravasation: case report and review of the literature. Austin J Orthopade & Rheumatol 2016; 3(1):1026. https://austinpublishinggroup.com/orthopedics-rheumatology/fulltext/ajor-v3-id1026.php. Accessed April 11, 2023.
8. **Fox AN, Villanueva R, Miller JL.** Management of amiodarone extravasation with intradermal hyaluronidase. Am J Health Syst Pharm 2017; 74(19):1545–1548. doi:10.2146/ajhp160737
9. **Roditi G, Khan N, van der Molen AJ, et al.** Intravenous contrast medium extravasation: systematic review and updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol 2022; 32(5):3056–3066. doi:10.1007/s00330-021-08433-4
10. **Nicola R, Shaqdan KW, Aran S, Prabhakar AM, Singh AK, Abujudeh HH.** Contrast media extravasation of computed tomography and magnetic resonance imaging: management guidelines for the radiologist. Curr Probl Diagn Radiol 2016; 45(3):161–164. doi:10.1067/j.cpradiol.2015.08.004
11. **Hwang EJ, Shin CI, Choi YH, Park CM.** Frequency, outcome, and risk factors of contrast media extravasation in 142,651 intravenous contrast-enhanced CT scans. Eur Radiol 2018; 28(12):5368–5375. doi:10.1007/s00330-018-5507-y
12. **Heshmatzadeh Behzadi A, Farooq Z, Newhouse JH, Prince MR.** MRI and CT contrast media extravasation: a systematic review. Medicine (Baltimore) 2018; 97(9):e0055. doi:10.1097/MD.0000000000010055
13. **Wang CL, Cohan RH, Ellis JH, Adusumilli S, Dunnick NR.** Frequency, management, and outcome of extravasation of nonionic iodinated contrast medium in 69,657 intravenous injections [published correction appears in Radiology 2015; 274(1):307]. Radiology 2007; 243(1):80–87. doi:10.1148/radiol.2431060554
14. **Loubani OM, Green RS.** A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care 2015; 30(3):653.e9–653.e6.53E17. doi:10.1016/j.jcrc.2015.01.014

Address: *Shraddha Narechania, MD, FCCP, Department of Internal Medicine, Campbell University, 143 Main Street, Buies Creek, NC 27506; drshraddhanarechania@gmail.com*