Oncology nurses and pharmacists often are given the responsibility of developing or updating institutional policies to manage vesicant chemotherapy extravasations. Antidote and treatment recommendations of vesicant chemotherapy manufacturers, antidotes and treatments approved by the U.S. Food and Drug Administration (FDA), and guidelines and recommendations made by professional oncology organizations are useful resources in this process. This article describes manufacturers’ recommendations, lists antidotes and treatments approved by the FDA, and reviews published guidelines and recommendations. Available antidote and treatment formulations and their preparation and administration also are discussed.

At a Glance
- Periodic publication of guidelines and recommendations and lack of knowledge of antidotes and treatments approved by the U.S. Food and Drug Administration (FDA) present challenges to developing institutional extravasation policies.
- Recommendations of professional oncology organizations vary in their content and may be inconsistent with those of vesicant chemotherapy manufacturers.
- Institutional policies and procedures for managing extravasations should be current and align with recommendations by drug manufacturers, the FDA, and professional oncology organizations.

Antidotes are agents that neutralize a poison or counteract its effects. They are used in oncology practice when vesicant chemotherapy extravasates from the vein or is administered inadvertently into tissue. Although several drugs and substances have been evaluated as vesicant extravasation antidotes and treatments, data on their safety and efficacy are limited and largely based on the results of animal studies and case reports (Wickham, Engelking, Sauerland, & Corbi, 2006).

In many institutions, oncology nurses and pharmacists develop or update institutional policies and procedures for managing vesicant chemotherapy extravasations. In some settings, chemotherapy guidelines and recommendations published by organizations are adopted for use. Challenges in policy development and guideline implementation include the periodic publication of organizational guidelines (new antidotes or treatments may become available after the publication date) and discontinued manufacturing of a recommended antidote (which occurred from 2001–2004 when Wydase®, the only hyaluronidase product available prior to 2001, was no longer manufactured by Wyeth).

Many interventions still used in clinical practice to treat extravasations are empirical and controversial (Wickham et al., 2006). Clinicians may be unaware that new treatments approved by the U.S. Food and Drug Administration (FDA) have been introduced. In addition, ambiguous and labor-intensive recommendations have been made. For instance, in the full prescribing information for vinorelbine, Bedford Laboratories (2005) stated, “since there are no established guidelines for the treatment of extravasation injuries with vinorelbine, institutional guidelines may be used” (p. 8). With such vague information, institutional policies are difficult to develop. Similarly, the International Society of Oncology Pharmacy Practitioners (2007) stated in its practice standards that, “the medical and pharmaceutical literature should be consulted and a consensus decision made about which agents to use to treat each extravasation” (p. 63). The approach is highly labor-intensive in any setting and may be impractical.

The challenges prompt the questions, “How can oncology nurses and pharmacists best develop or update institutional extravasation policies?” and “What resources are available to assist them in this process?” Because vesicant chemotherapy extravasations rarely occur and antidotes are infrequently administered, clinicians likely will be referring to institutional policies in the event of a vesicant extravasation; therefore, the policies must be current and clearly delineated.
Resources for Developing and Updating Institutional Policies

Manufacturers of Chemotherapy Vesicants

Merck and Co., Inc. (2002), manufacturer of Mustargen® (mechlomethamine HCl for injection), stated that extravasation of mechloethamine, commonly known as nitrogen mustard, results in painful inflammation that progresses to induration and sloughing of tissue. Prompt infiltration of the area with sterile isotonic sodium thiosulfate (1/6 molar) solution and application of an ice compress for 6–12 hours is recommended.

Bedford Laboratories (2001), manufacturer of vinblastine sulfate for injection, and Mayne Pharma, Inc. (2004), and SICOR Pharmaceuticals, Inc. (2003), manufacturers of vincristine sulfate injection, stated that extravasation of those plant alkaloids may cause considerable irritation. If extravasation occurs, administration of the agents should be discontinued immediately and any remaining portion of the dose should be administered into another vein. Local injection of hyaluronidase and application of moderate heat to the area of leakage help disperse the drug and minimize discomfort and the possibility of cellulitis.

Bedford Laboratories (2005), manufacturer of vinorelbine injection (also a plant alkaloid), stated that vinorelbine extravasation may cause considerable irritation, local tissue necrosis, and thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately and any remaining portion of the dose should be administered into another vein. As stated previously, Bedford Laboratories recommended that institutional guidelines may be used because no established guidelines exist for the treatment of extravasation injuries with vinorelbine.

Bedford Laboratories (2006), manufacturer of doxorubicin, stated that the benefit of the local administration of drugs in treating a doxorubicin extravasation has not been clearly established. The manufacturers of the other available anthracyclines (daunorubicin, idarubicin, epirubicin) acknowledge the potential of the agents to cause tissue necrosis but do not mention use of any local antidotes or treatments (Bedford Laboratories, 2007, 2008; Pfizer, 2007).

U.S. Food and Drug Administration

Sodium thiosulfate (antidote to mechlorethamine extravasation) and hyaluronidase (antidote to plant alkaloid extravasation) are approved by the FDA. However, their indications are not vesicant extravasation antidote-specific. The only FDA-approved drug specifically indicated for extravasation treatment is Totect® (dexrazoxane for injection, TopoTarget USA); sodium thiosulfate and hyaluronidase are not FDA approved for extravasation treatment indications. Totect is administered systemically as an IV infusion, and its sole indication is the treatment of extravasation resulting from IV anthracycline chemotherapy (FDA, 2008).

Sodium thiosulfate, in conjunction with sodium nitrite, is indicated for use as an antidote in the treatment of cyanide poisoning. Hyaluronidase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents (FDA, 2008).

Professional Organizations

The Oncology Nursing Society’s Chemotherapy and Biotherapy Guidelines and Recommendations for Practice (3rd ed.) includes recommendations to treat anthracycline extravasations with Totect, administer the antidote sodium thiosulfate when mechlorethamine extravasations occur, and administer the antidote hyaluronidase when plant alkaloid extravasations occur (Polovich, Whitford, & Olsen, 2009).

The European Oncology Nursing Society (EONS) published extravasation guidelines in four languages in 2007 (Wengstrom & Margulies, 2008). Savene® (TopoTarget A/S, 2006), the equivalent of Totect in the United States, is recommended for anthracycline extravasation treatment. Sodium thiosulfate is not recommended for mechlorethamine extravasations “due to lack of evidence”; however, further rationale for the recommendation is not discussed in the EONS guidelines (p. 25). Hyaluronidase is “suggested as a possible antidote in many literature sources” and “due to lack of evidence it is recommended that this is further studied” (EONS, p. 25).

The United Kingdom ONS adapted the EONS guidelines and published UKONS Anthracycline Extravasation Management Guidelines in January 2008. Savene is recommended for anthracycline extravasations exceeding 1.5 ml, with “volumes based on clinical judgment” (UKONS, p. 5).

The American Society of Clinical Oncology, Hematology/Oncology Pharmacy Association, International Society of Oncology Pharmacy Practitioners, Multinational Association of Supportive Care in Cancer, and National Comprehensive Cancer Network have not developed or published vesicant chemotherapy extravasation management guidelines or recommendations (Morganstern & Held-Warmkessel, 2008).

Formulations and Mechanisms of Action

Sodium thiosulfate is available as a 10% or 25% solution (American Regent, Inc., 2003) as well as a 25% solution in cyanide antidote kits that contain two vials of sodium nitrite and two vials of sodium thiosulfate injection, USP 12.5 g in 50 ml of sterile water for injection (Taylor Pharmaceuticals, 2006). Although its exact mechanism of action is unknown, sodium thiosulfate is believed to chemically neutralize the reactive alkyling species of mechlorethamine and reduce the production of hydroxyl radicals that cause tissue injury (Dorr, Sobel, & Alberts, 1988).

Mechlorethamine rarely is used in clinical practice. In institutions still using it, clinicians should consider implementing a process that ensures the antidote for mechlorethamine extravasation (sodium thiosulfate) has not expired. Some institutions have implemented the procedure of sending sodium thiosulfate to the patient care area whenever mechlorethamine is administered.

Four formulations of hyaluronidase are available in the United States. Three are animal-derived products: Amphastar® (Amphastar Pharmaceuticals, Inc.) and Hydase® (Akorn, Inc.) are bovine (cow) derivatives, and Vitrase® (ISTA Pharmaceuticals) is an ovine (sheep) derivative. Hylenet® (Baxter Healthcare Corporation) is a purified preparation of the enzyme recombinant human hyaluronidase. Several other hyaluronidase formulations are available globally, such as Hylase® (sanoft-aventis, Australia) and Hynidase (Shreya Life Sciences, India). Hyaluronidase product selection is based on prescriber preference; some
Prescribers prefer a recombinant human product rather than animal-derived products to lessen the likelihood of local injection reactions.

Hyaluronidase is an enzyme that modifies the permeability of connective tissue through hydrolysis of hyaluronic acid. It helps disperse plant alkaloid vesicants that have extravasated into the tissue and promotes their absorption (Dorr, 1990).

The Totect anthracycline extravasation treatment kit is available in the United States and its equivalent, Savene, is available in Europe and the United Kingdom. The kits contain a complete three-day treatment and are packaged for single-patient use. The mechanism by which Totect diminishes tissue damage resulting from the extravasation of anthracycline vesicants is unknown (TopoTarget USA, 2006). Because it is a prodrug analog of the metal chelator ethylenediaminetetraacetic acid, Totect may act by removing iron from iron-anthracycline complexes that form in the tissue, preventing formation of damaging reactive oxygen species (Hasinoff, 2008).

### Preparation and Administration

Preparation and administration instructions for vesicant chemotherapy extravasation antidotes and treatments are described in Figure 1. The antidotes sodium thiosulfate and hyaluronidase are locally injected into the extravasation area. Although the antidotes are mentioned in a number of articles and guidelines, details of how they should be administered often are inconsistent or not mentioned. The EONS (2007) guidelines, for instance, recommended that hyaluronidase be locally injected into “the subcutaneous tissue surrounding the extravasated area” (p. 23). Ener, Meglathery, and Styler (2004) suggested that the antidotes be given “into the extravasation site through the existing IV line and/or if the line has been removed, in a clockwise manner” (p. 861). Administering an antidote into the existing IV line is based on the presumption that the tip of the IV device lies in the subcutaneous tissue, which is the intended injection site. However, the tips of peripheral and central IV devices may actually be in the venous system (e.g., when central line catheter nicking causes the extravasation or when repeated venipuncture occurs prior to peripheral IV placement). The antidote would then be administered via IV instead of the intended subcutaneous route of administration. Furthermore, much of the antidote could remain in the device if the antidote is injected through the device prior to its removal. Therefore, removing the peripheral IV device or noncoring implanted port needle, then locally injecting the antidote into the extravasation area may be preferable.

Totect or Savene is a systemic anthracycline extravasation treatment administered by IV infusion in a large vein in an area away from the extravasation site (e.g., opposite arm). If the opposite arm cannot be used for venipuncture, clinical judgment should be used to identify a site above the anthracycline extravasation area where a peripheral IV device (or peripherally inserted central catheter) can be inserted (Schulmeister, 2007).

### Summary

Oncology nurses frequently administer vesicant chemotherapy and are aware that a potential complication of vesicant administration is extravasation. Fortunately, extravasations are rare events.

### Sodium Thiosulfate

- Prepare a 1/6 molar solution.
  - If 10% sodium thiosulfate solution, mix 4 ml with 6 ml sterile water for injection.
  - If 25% sodium thiosulfate solution, mix 1.6 ml with 8.4 ml sterile water.
- Store at room temperature from 15°C–30°C (59°F–86°F).
- Inject 2 ml sodium thiosulfate solution for each ml of mechloretamine suspected to have extravasated. Inject the solution into the extravasation site using a 25 gauge or smaller needle (change needle with each injection).

### Hyaluronidase

- Amphadase® (Amphastar Pharmaceuticals, Inc.): Vial contains 150 units per 1 ml. Do not dilute. Use solution as provided. Store in refrigerator at 2°C–8°C (36°F–46°F).
- Hydase® (Akorn, Inc.): Vial contains 150 units per 1 ml. Do not dilute. Use solution as provided. Store in refrigerator at 2°C–8°C (36°F–46°F).
- Vitrase® (ISTA Pharmaceuticals): Vial contains 200 units in 2 ml vial. Dilute 0.75 ml of solution with 0.25 ml of 0.9% sodium chloride (final concentration is 150 units per 1 ml). Store in refrigerator at 2°C–8°C (36°F–46°F).
- Administer 1 ml of the hyaluronidase solution as five 0.2 ml injections into the extravasation site using a 25 gauge or smaller needle (change needle with each injection).

### Totect®

- The recommended dose of Totect® (TopoTarget USA) is based on the patient’s body surface area.
  - Day 1: 1,000 mg/m²
  - Day 2: 1,000 mg/m²
  - Day 3: 500 mg/m²
- The maximum recommended dose is 2,000 mg on days 1 and 2 and 1,000 mg on day 3. The dose should be reduced 50% in patients with creatinine clearance values less than 40 ml per minute.
- Each vial of Totect 500 mg must be mixed with 50 ml diluent. The patient’s dose of Totect is then added to a 1,000 ml sodium chloride infusion bag for administration.
- The Totect emergency treatment kit contains 10 vials of Totect 500 mg and 10 vials of 50 ml diluent and is stored at 25°C (77°F).
- The first Totect infusion should be initiated as soon as possible and within six hours of the anthracyline extravasation. Totect should be infused over one to two hours in a large vein in an area away from the extravasation area (e.g., opposite arm).

**Note:** Always consult the full prescribing information for any medication prior to its preparation and administration.

### Figure 1. Preparation and Administration Instructions for Vesicant Chemotherapy Extravasation Antidotes and Treatments

**Note:** Based on information from Akorn, Inc., 2007; American Regent, Inc., 2003; Amphastar Pharmaceuticals, Inc., 2005; Baxter Healthcare Corporation, 2006; ISTA Pharmaceuticals, 2004; TopoTarget USA, 2006.

When they inadvertently occur, nurses and pharmacists often consult institutional extravasation management policies and procedures. These policies and procedures should be current and align with recommendations from vesicant chemotherapy manufacturers, the FDA, and professional oncology organizations.
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