

CLINICAL CHALLENGES

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Mitoxantrone-Induced Extravasation

Case Study

V.H., a 53-year-old male with a diagnosis of progressive relapsing, remitting multiple sclerosis and a history of diabetes, presented to the clinic for his trimonthly dose of mitoxantrone (Novantrone®, Immunex, Thousand Oaks, CA) 12 mg/m² immunosuppressive therapy. A peripheral 22-gauge IV was started on the dorsum of the left hand and verified for patency by establishing a good blood return and checking for signs of infiltration. A 0.9% sodium chloride flush line was started followed by the one-hour piggyback mitoxantrone infusion. Thirty minutes into the infusion, the patient noted burning, pain, and swelling at the IV site. He informed the nurse of the symptoms immediately. The infusion was stopped promptly, and the supervising nurse and the patient's physician were notified. At the time of this event, mitoxantrone was labeled as an irritant at this ambulatory infusion center. In the case of extravasation, the protocol dictated that the infusion be stopped and ice applied immediately. In addition, V.H. was instructed to apply ice to the site for 48 hours with the arm elevated. At his next appointment, the patient denied pain at the infusion site although he had a 1 cm by 1 cm area of discoloration. Three months later, after intermittent therapy with antibiotics and topical ointments, the site had developed an eschar over a 2 cm by 2.5 cm area of underlying necrosis. A plastic

surgery consultation was obtained. The plastic surgery team monitored the necrotic site for another two months without intervention (see Figure 1). During this time, the lesion extended to a 3 cm by 3 cm area of necrosis mandating that V.H. undergo debridement and skin grafting to promote healing of the necrotic site (see Figure 2).

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Clinical Problem Solving

Responding to this clinical interview by Enza Luke, RN, MSN, OCN®, is Linda Person, RN, MSN, AOCN®, an advanced practice nurse at the University of Southern California/Kenneth Norris Comprehensive Cancer Center and Hospital in Los Angeles.

What are some of the most important factors associated with chemotherapy extravasation?

Numerous factors have been identified with the incidence of vesicant extravasation; among them are the skill of the nurse performing the venipuncture and the method used for administering the drug. Nurses should be trained in performing venipuncture and managing all types of venous access devices, and their skills should be assessed annually. The knowledge to administer vesicant agents safely and the expertise to prevent and assess extravasation must be validated by observation of behavioral performance (Camp-Sorrell, 1998). These standards of practice have been outlined clearly in the Oncology Nursing Society's chemotherapy and biotherapy guidelines (Brown et al., 2001). The most important of these skills are using the forearm, not the hand, to establish a peripheral line; administering the vesicant drug via a bolus push through a free-flowing IV line; checking for a blood return every 2–3 cc or hourly for continuous infusions through a central line; and securing the needle and all connections with tape. Inadvertent needle dislodgment



Figure 2. Patient Approximately Two Weeks Following Skin Graft

or migration may cause extravasation or infiltration.

Accessing veins in areas with decreased circulation or sensation should be avoided when administering any drug that can cause tissue necrosis if extravasated. Additionally, veins located in close proximity to superficial nerves and tendons should be avoided if possible. These areas include veins on



Figure 1. Patient Approximately Five Months After Extravasation

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the dorsum of the hand as well as the wrist. However, with the majority of patients receiving combination regimens, the patency of veins in the hand sometimes makes them the only feasible option. Areas of flexion such as the antecubital fossa should not be used for the IV infusion of vesicants because extravasations in this area can severely compromise function and complicate surgical interventions (Camp-Sorrell, 1998). Needle dislodgement from an implanted port or a vein can cause extravasation. Additionally, damage, breakage, or separation of any vascular access device within the vessel can cause extravasation (Camp-Sorrell; Hadaway, 2002).

The condition of the patient's veins may increase the risk for extravasation. Small fragile veins as well as veins with multiple venipuncture scars are at high risk for leaking. Chronic medical conditions such as malnutrition, diabetes mellitus, autoimmune diseases, and certain medications (e.g., prednisone) also can jeopardize venous access (Skokal, 2001); therefore, nurses must be familiar with each patient's medical history.

What is the most significant sign of chemotherapy extravasation and how can it be differentiated from a localized irritation or "flare" reaction?

Nurses should be skilled in recognizing the difference between a localized irritation or

"flare" response and signs of a true extravasation. Severe pain at the needle site is the hallmark of an extravasation; the pain associated with an irritation caused by infiltration most often is reported as aching or tightness at the site and can be accompanied by redness or darkness along the vein (Goodman & Peterson, 1997). A flare reaction typically is not associated with pain but most often is characterized by red blotches around the needle site and streaking or itching along the vein (Goodman & Peterson). Nurses must be aware that in all three cases—extravasation, vein irritation, and flare reactions—a blood return may be present. In addition, nurses must understand that medications given prior to chemotherapy to prevent adverse side effects can cause somnolence or altered mental status, preventing patients from feeling or reporting early signs of extravasation.

Swelling usually occurs if the drug leaks into the surrounding supportive tissues; however, this symptom can be absent in an extremely dehydrated or malnourished patient. Blotchy redness around the needle site does not always present at the time of extravasation and may indicate localized irritation. Actual ulceration may develop insidiously in 48–96 hours with vesicant extravasation.

Which factors determine the degree of tissue damage with extravasation?

The severity of tissue damage that follows extravasation depends on the drug's vesicant

potential, the amount of drug extravasated, and the needle placement (Hadaway, 2002). Ulceration is not always immediately evident and may be delayed by weeks or months (Brown et al., 2001). The pathophysiology of tissue damage is the result of the vesicant drug binding to host DNA or microtubules in a process that is self-perpetuated when the vesicant is released as the affected cells are lysed (Langstein, Duman, Seelig, Butler, & Evans, 2002). Other antineoplastics or vesicants may cause tissue damage through nonspecific inflammatory reactions (Langstein et al.).

What is the current management of chemotherapy extravasation?

Because experimenting with extravasation and antidote management in humans is ethically repugnant, evidence in the literature is lacking regarding the appropriate antidotes for specific medications. Most studies have been conducted in animal models or anecdotally reported in humans; therefore, true efficacy is unknown (Camp-Sorrell, 1998; Hadaway, 2002). Nonetheless, hyaluronidase has been used successfully for extravasation of vinca alkaloids such as vincristine and vinblastine (Camp-Sorrell). Additionally, dimethyl sulfoxide has been studied for its antioxidant action against free radical-producing anthracyclines, such as doxorubicin.

The most important factor in extravasation management is rapid recognition and

Clinical Highlights: Extravasation

Definition: Extravasation is the inadvertent administration of a vesicant solution into surrounding healthy tissue. A vesicant is a solution capable of causing destruction of healthy tissue if it escapes from the circulation into surrounding tissue (Hadaway, 2002).

Pathophysiology: Cellular damage begins with an acute inflammatory response caused by the noxious accumulation of the vesicant in the surrounding tissue. Mast cell degranulation, the activation of the plasma system, and the release of subcellular components from the damaged cells cause increased vascular permeability and edema (Rote, 1998). When fluid inside a compartment increases, the venous end of the capillary is compressed and the vessel is unable to carry away excessive fluid. The hydrostatic pressure increases, creating a compartment syndrome. Arteriolar compression, vascular spasm, necrosis, and tissue damage ensue (Hadaway, 2002). Functional muscular changes can occur within 4–12 hours of injury. Ischemic nerve damage can occur within 24 hours, causing functional loss of the affected extremity (Hadaway).

Risk factors: Chemotherapy extravasation can be a serious complication of various curative therapies and can cause serious functional loss of an extremity. Risk factors can be related to poor technique and inexperience, a poorly secured needle, or patient variables such as poor nutritional status, fragility of skin and connective tissue as a result of disease or therapy, and sclerosed or tortuous veins. Many of these factors are seen in patients with cancer, diabetes, and atherosclerosis (Skokal, 2001).

Clinical findings: Severe pain at injection site, burning, erythema, swelling, and inadequate blood return may result; however, good blood return does not indicate that extravasation is not occurring.

Differential diagnosis: Among some of the differential diagnoses to consider in this case are phlebitis, vein irritation, flare reaction, localized allergic reaction, and extravasation.

Treatment: Stop the infusion, aspirate any residual drug from the IV with an empty syringe, and leave the needle in place for administration of an antidote if prescribed. If appropriate, aspirate any bleb that may appear at the infusion site. Follow the recommended standard of the institution for further management. Remove the needle without applying

undue pressure at the IV site. Apply hot or cold compresses according to institutional policy. Notify the prescribing physician and document accordingly. Arrange a plastic surgery consultation when warranted.

Prevention: Expert IV skills, education, and training in chemotherapy administration, in addition to knowledge of vesicant agents and specific vesicant protocols, will help to decrease the number and severity of extravasations in clinical practice. Moreover, preparedness and knowledge of extravasation management can assist chemotherapy nurses in the swift identification and management of extravasations. At the start of any chemotherapy infusion, identify any patients who may be at high risk for extravasation such as patients with poor venous access, frail veins, etc.

Hadaway, L.C. (2002). I.V. infiltration: Not just a peripheral problem. *Nursing*, 32(8), 36–42.

Rote, N.S. (1998). Inflammation. In K.L. McCance & S.E. Huether (Eds.), *Pathophysiology* (pp. 205–236). St. Louis, MO: Mosby.

Skokal, W.A. (2001). Drug disasters: Extravasation. *RN*, 64(9), 56–62.

initiation of therapy to prevent further tissue damage. Continuous monitoring and keen assessment by the nurse infusing the chemotherapy agent are essential. Once an extravasation or infiltration of mitoxantrone is suspected, the infusion must be stopped and any residual drug must be removed through the IV catheter (Camp-Sorrell, 1998). Apply ice to the affected area immediately, and inform the physician who prescribed the chemotherapy. According to Immunex (2002), the affected arm should be elevated and the site of a suspected extravasation should be monitored closely for signs of necrosis.

Which classification of chemotherapeutic agent is mitoxantrone?

Mitoxantrone's mechanism of action occurs within the cell; however, most experts agree that it should be considered an antitumor antibiotic (Gonsette, 2003; Immunex, 2002). This agent has many properties that suppress the immune system, specifically T cell deactivation, and has proven to be an effective treatment for multiple sclerosis (Hartung et al., 2002). As with the majority of antitumor antibiotics, mitoxantrone does not have a reliable antidote that can be used if infused into tissues. Tissue damage, although rarely reported, is caused by the binding nature of the drug when exposed to the tissues. Continued tissue destruction may result in a necrotic wound that requires surgical intervention (Harris & Moss, 2002).

Some researchers have suggested that mitoxantrone only causes serious tissue damage when administered in a concentrated dose (Brown et al., 2001). However, as in V.H.'s case, this statement is controversial because the drug was administered as a diluted IV piggyback infusion. In some literature, mitoxantrone is considered an irritant, whereas in many others, it is reported as a vesicant (Alley, Green, & Schuchter, 2002; Brown et al.; Langstein et al., 2002). Despite the fact that Immunex (2002) has not classified mitoxantrone as a vesicant agent, the manufacturer noted that extravasation can cause tissue necrosis.

Two important lessons can be learned from V.H.'s case study. First, nurses administering chemotherapeutic agents must be skilled and cautious with all agents classified as irritants or vesicants because patients' integument and medical status may place them at a higher risk for complications regardless of how the drug has been classified in the literature. Second, case reports are needed regarding this increasingly used chemotherapy agent to support standards of practice in its delivery and the efficacious treatment in the event of extravasation.

How are extravasation standards of care developed and implemented?

Dorsett (2000) defined standards of nursing practice as the principles that must be

continuously tested, redefined, and verified by research. Additionally, standards of care serve as a model to facilitate the delivery and evaluation of optimal nursing care based on the nursing process. Standards provide a description of minimum acceptable practice levels for nurses. A clinical problem or concern often stimulates the need for standardization of care. Nursing now is basing standards of practice on evidence (Dorsett). In the institution treating V.H., clinicians and pharmacists had reviewed available literature and research studies on this drug and developed a protocol for the management of vesicant extravasation. When timely identification and treatment are known by clinical staff at the bedside, patient outcomes can be more positive.

Standards of nursing practice reflect the expected competencies of nursing performance and are viewed in legal terms as a model for established practice (Camp-Sorrell, 1998). For example, a standard of practice for the delivery of vesicants is that this classification of medications should be administered as a bolus and pushed through a free-flowing IV line. Standards of chemotherapy administration practice also define the safe handling and administration of medications, such as evaluating IV patency and assessing for signs of infiltration or extravasation (Brown et al., 2001). Based on a standard of practice, guidelines and protocols can be developed and can support decisions in the delivery of patient care, such as the prevention of mitoxantrone extravasation.

When V.H. complained of a painful burning sensation, the nurse immediately stopped the infusion and managed the situation per protocol. Ice was applied, the affected arm was elevated, and the physician was notified. The patient then was advised to apply ice to the site for 48 hours after discharge. This protocol was based on the limited information in the literature regarding mitoxantrone extravasation management. However, because of the patient's history of diabetes mellitus, a chronic illness that can delay or even interfere with healing, this incident could have been monitored more carefully by taking initial photographs of the site and followed with more aggressive, consistent medical interventions.

The best treatment for dealing with extravasation is prevention. In addition, clinicians need to document and report extravasation incidents to prevent future events and to improve clinical outcomes. Nurses are in a key position in any institution to analyze sentinel events and revise protocols and procedures to preclude clinical errors from reoccurring. Following this case, the clinical nurse specialist notified both the institution's pharmacy and the U.S. Food and Drug Administration. To support evidence-based practice, mitoxantrone was added to the list of vesicants in the institu-

tion's policy. Therefore, in the institution, the drug now is administered as an IV push through a free-flowing IV line following vesicant standards. In some institutions, protocols continue to label mitoxantrone as an irritant, not a vesicant, and the drug is administered as an IV piggyback infusion. More studies and anecdotal information regarding the administration and extravasation of mitoxantrone are needed, especially in light of an increased number of patients receiving this medication and, as in this case, the scope of practice expanding beyond the field of oncology nursing.

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