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The Danger of 10% Intravenous Calcium Chloride Extravasation.

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The Case

A 52-year-old man with a history of lymphoplasmacytic lymphoma was admitted to the hospital with fever, rigors, and hypotension. He had respiratory failure and required intubation and mechanical ventilation. He was diagnosed with septic shock and underwent vigorous fluid resuscitation and antibiotic therapy. He required both dobutamine and vasopressin. One day after admission, he suffered an infiltration from an infusion of calcium chloride into the dorsum of his left hand. After resuscitation and stabilization, he was noted to have venous congestion and soft tissue damage to the left fourth finger. Multiple services were contacted to assist with management of this complicated wound. After conservative treatment for nearly three weeks, the wound did not show any appreciable healing, and the affected finger was surgically amputated.

The Commentary

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Background

This case represents a known but generally preventable complication of calcium chloride infusion, eventually necessitating surgical amputation of the patient's left fourth (ring) finger. Although it is often necessary to administer intravenous calcium chloride to critically ill patients, extreme care must be taken to ensure that it is not injected into extravascular tissues. To prevent iatrogenic injuries of this type, physicians, nurses, and pharmacists must work together to understand medication side effects, select lower-risk formulations and intravenous lines, and recognize extravasation immediately.

Calcium chloride 10% injection solution is approved by the FDA to treat severe hypocalcemia or other conditions that require a rapid increase of plasma calcium levels. It is one of the first line therapies given in emergent cases of severe hyperkalemia or calcium-channel-blocker or beta-blocker overdose.[1,2] However,

it is contraindicated in cardiac resuscitation in the presence of ventricular fibrillation, or in patients at risk for digitalis toxicity.[1] In addition, calcium chloride is not recommended in the treatment of asystole or electromechanical dissociation (in the absence of other indications, such as severe hyperkalemia).[1] The solution is preferably administered by slow intravenous (IV) injection at a rate not to exceed 1mL/min **via central or deep vein.** When the infusion exceeds this maximum rate, it may cause lowering of blood pressure.[1]

Calcium chloride is considered a vesicant, an agent capable of causing severe irritation, skin blistering, and tissue destruction,[2] partly due to its relatively high osmolarity (i.e., 2040 mOsm/L).[3] Furthermore, a locally high concentration of dissociable calcium salts may cause precipitation of proteins;[4] as a result, calcium chloride must not be injected directly into tissues.[1] Multiple case reports of severe necrosis and sloughing or iatrogenic calcinosis cutis due to calcium chloride or calcium gluconate extravasation have been published.[5,6] Therefore, great care should be implemented to avoid accidental infusion into perivascular tissue.

A recent retrospective cohort study evaluated the safety of 10% calcium chloride administration via peripheral venous catheters in emergency settings. Among 43 patients with 72 IV administrations of 10% calcium chloride, 6% of the administrations (in 3 patients) were associated with low-grade infusion-related adverse events (IRAE). The median time to IRAE was 71 hours and no patient received plastic surgery consultation or medications, such as hyaluronidase, to prevent skin injury.[3] This observed incidence of IRAE with peripherally administered 10% calcium chloride was consistent with previous reports of IRAE rates between 1% and 17%.[3] Therefore, administration of 10% calcium chloride via peripheral venous catheter may be feasible, with an acceptable complication rate, offering an alternative in emergent cases when central venous access is not available. However, the authors suggested using a catheter with the largest possible bore in the most proximal accessible vein and exercising great caution before adopting this method of administration in non-emergency settings.[3]

During infusion of fluids, the intravenous catheter can become dislodged and/or penetrate through the wall of the vein. Erosion of the venous wall may be induced by endovascular inflammation from movement of the catheter inside the vessel, by caustic effects from IV medications, or by needle injury from previous catheter insertions.[7] As a vein's capacity to retain and carry fluid is compromised, fluids leak into the surrounding soft tissue. When the leaking fluid is a non-vesicant solution or medication, this process is called infiltration; when it is a vesicant medication, it is called extravasation.[8] Failures of IV catheters are very common in clinical settings, with rates of 15.7% to 33.8% in the adult population[7] and 2.9% and 2.3%, for infiltration and extravasation respectively, in the pediatric (age ?12) population.[9]

Tissue damage from extravasation of vesicants may be limited to epidermal damage or may extend deeper into muscle and fascia, resulting in compartment syndrome and potentially loss of the appendage. Extravasation may be categorized into 4 stages according to the severity of the injury, as described in **Table 1**.

Table 1. Staging of Extravasation[5]

Stage	Description

1	• Pain at the infusion site • Localized swelling affecting less than 10% of extremity (above or below the infusion site) • No erythema
2	• Pain at the infusion site • Localized swelling affecting up to 25% of extremity (above or below site) • Slight erythema (at the central area of the site of extravasation) • Pulses are detectable below the site • Rapid (1-2 s) capillary refill below the site
3	• Pain at the infusion site • Moderate swelling (affecting 25%-50% of extremity above or below site) • Marked erythema, which spreads beyond the central area of the site of extravasation • Pulses are still detectable below the site • Rapid (1-2 s) capillary refill below site • Skin cool to touch • For vasopressor extravasation -- blanching effects may be observed
4	• Pain at the infusion site • Severe swelling affecting >50% of extremity (above or below site) • Severe erythema extends beyond borders of the swelling • Decreased or absent pulse below site • Prolonged capillary refill (>4 seconds) • Skin cool to touch • Blanching effects even from the non-vasopressor extravasation • Breakdown of skin including blistering or necrosis

By contrast, leakage of irritant medications causes tissue inflammation or swelling, but the local reaction can usually be resolved with minimal intervention (**Table 2**).[10]

Table 2. Selected list of irritants[11]

Irritants

Alkylating agents • Carboplatin • Carmustine • Cisplatin • Cyclophosphamide • Dacarbazine • Ifosfamide • Melphalan • Oxaplatin • Thiotepa
Antimetabolites • Cytarabine • Fludarabine • 5-Fluoruracil • Gemcitabine • Methotrexate
Others • Bleomycin • Etoposide • Irinotecan

Approach to Improving Safety and Patient Safety Target

As this case highlights, selecting the safest feasible mode of infusion for vesicant medications can prevent catastrophic soft tissue damage. Safe infusion of these medications requires health care providers to understand their relevant properties, and infuse them through a central venous catheter, if possible, over an appropriate amount of time. When choosing a peripheral vein, a large vein that can accommodate a large bore catheter may reduce the concentration of irritant or vesicant fluid entering the vessel.

Nurses should understand the most frequent risk factors[9] associated with extravasation, which include:

- Prior multiple venipunctures
- Fragile small veins
- Deficit of sensation
- Limited selection of veins due to lymph node dissection or edema or limb amputation
- Impaired or altered mental status
- Insufficiently secure IV catheter

- Administration sites at the dorsum of the hand, or wrist

Early and accurate identification of extravasation and infiltration is crucial. When a patient complains of pain or discomfort around the IV site, the infusion should be stopped, and the site assessed. In addition, hourly rounding and inspection of the IV site during high-risk infusions may be beneficial. Any delay of appropriate treatment may lead to irreversible consequences. Each vesicant has its own ***necrosis interval***, which is the time between extravasation and irreversible tissue necrosis.[4] If interventions are implemented during this period to counteract the effects or remove the offending agent, necrosis may be prevented. However, when extravasation is recognized late, prevention of tissue damage may no longer be possible.[4] Unfortunately, the necrosis interval of each vesicant has not yet been determined, except that it has been estimated at 4-6 hours for vasopressors.[4]

Since each episode of extravasation is unique, many factors can influence the extent of tissue injury, including the patient's age, weight, skin integrity, comorbidities, anatomic anomalies, site of extravasation, communication barriers, care setting, response to current treatment, and the amount, concentration, and identity of the vesicant.[4] Prompt consultation with a pharmacist and/or physician with specialized training is advisable to verify the recommended antidote and type of thermal compression when needed (**Table 3**).

Table 3. Selected list of vesicants and their antidotes.[4,6]

<table>
<tr><th>Vesicants</th><th>Antidote</th><th>Thermal Compression</th></tr>
<tr><td>High osmolarity leading to tissue damage</td><td></td><td rowspan="10">Warm</td></tr>
<tr><td>Aminophylline (170mOsm/L)</td><td rowspan="2">Hyaluronidase</td></tr>
<tr><td>Ampicillin 50mg/mL</td></tr>
<tr><td>Calcium chloride 10%;
or calcium gluconate</td><td>Hyaluronidase
or sodium thiosulfate</td></tr>
<tr><td>Dextrose ?10% (505 mOsm/L)</td><td rowspan="5">Hyaluronidase</td></tr>
<tr><td>Nafcillin 40mg/mL</td></tr>
<tr><td>Parenteral nutrition (>900mOsm/L)</td></tr>
<tr><td>Potassium chloride 20mEq/100mL;
40mEq/100mL</td></tr>
<tr><td>Sodium chloride ?3%</td></tr>
<tr><td>Low or high pH leading to tissue damage</td><td></td><td></td></tr>
<tr><td>Dantrolene (pH 9.5 - 10.3)</td><td rowspan="4">Hyaluronidase</td><td rowspan="4">Warm</td></tr>
<tr><td>Doxycycline (pH 1.8 – 3.3)</td></tr>
<tr><td>Esmolol (pH 4.5 – 6.5)</td></tr>
<tr><td>Gentamicin (pH 3 – 5.5)</td></tr>
</table>

Vesicants	Antidote	Thermal Compression
Phenytoin (pH 10 – 12.3)		
Promethazine (pH 4.0 – 5.5)		
Vancomycin (pH 2.5 – 4.5)		
Vasoconstriction leading to tissue damage ***Dobutamine***		
Dobutamine	1st line: Phentolamine 2nd line: terbutaline or nitroglycerin	Warm
Dopamine		
Epinephrine		
Norepinephrine		
Phenylephrine	1st line: Phentolamine 2nd line: Nitroglycerin	
Vasopressin	1st line: Nitroglycerin 2nd line: Phentolamine or terbutaline	
Unknown mechanism of tissue damage		
Amphotericin (pH 5 – 7)	Hyaluronidase and flush out	Warm
Metronidazole (pH 4.5 – 7)	Hyaluronidase	
Penicillin (pH 5 – 8.5)		
Valproate (pH 7.6)	Hyaluronidase and flush out	Cold
Chemotherapy Agents[12,13]		
Alkylating agents: • Nitrogen mustard	• Sodium thiosulfate • Cold pack & extremity elevation	Cold
Anthracyclines: • Daunorubicin • Doxorubicin • Epirubicin • Idarubicin	• Dexrazoxane • Cold pack & extremity elevation	Cold
Antitumor antibiotics • Dactinomycin • Mitomycin-C	• No antidote • Cold pack & extremity elevation	Cold

Vesicants	Antidote	Thermal Compression
Taxanes • Docetaxel • Paclitaxel	• No specific antidote • Suggested hyaluronidase & warm compress applied 20min QID x 3 days.7 • DMSO applied topically 3x every 45 minutes plus oral steroid and diclofenac were successful in managing docetaxel extravasation.7	Cold
Vinca Alkaloids • Vinblastine • Vincristine • Vinorelbine • Vindesine	• Hyaluronidase • Heat pack & extremity elevation	Warm

Systems Change Options and Quality Improvement Approach

Based on the above case presentation, multiple system changes could be implemented to alert nurses and other health care providers while handling vesicants. First, vesicants may be labeled in the pharmacy with an auxiliary label indicating “Vesicant” to alert nurses handling the medication. Second, alert messages may be built into mobile, automated drug dispensing machines. When nurses remove an IV fluid or injectable vesicant from a medication dispensing cabinet or refrigerator, an alert message should be triggered indicating: “This is a vesicant – Administering through a central line may be required.” Third, before infusing a vesicant, the nurse must scan the barcode on the product, which is linked to the electronic Medication Administration Record (eMAR). At this step, a similar alert message could be built into the eMAR. Lastly, this alert message may also be added to the pump library, to be delivered to the nurse when the pump is programmed for infusing a vesicant.

In addition, nurses administering intravenous medications should be familiar with, and have access to, drug information resources such as Micromedex, Lexicomp, Epocrates, or other reputable online references. Typically, the contraindication section or black-box warning (BBW) of a vesicant product indicates the deleterious effects of extravasation caused by the agent. Health care providers, including physicians, nurses, and pharmacists, should be familiar with institutional policies and procedures regarding the handling of vesicants. Training modules covering these policies and procedures, including appropriate approaches to infiltration or extravasation, should be completed during the onboarding process for new employees and regularly thereafter. Effective management and prevention of injury from extravasation of vesicants requires knowledge of risk factors, early recognition and prompt intervention.

Take Home Points

- Calcium chloride (10%) is considered a vesicant, an agent capable of causing severe irritation, blistering of skin, and tissue destruction.
- During infusion of fluids, IV catheters can become dislodged and/or penetrate through the venous wall, resulting in infiltration when the leaking fluid is a non-vesicant solution or medication, and extravasation when the fluid is a vesicant medication.
- Correct identification of IV fluids as irritants or vesicants is important to guide how the fluid is handled and how the infusion is managed.
- Vesicants should be infused via a central line or by a large-bore IV catheter placed in a deep vein.
- Nurses should check the integrity and confirm the placement of vascular access devices, followed by rounding frequently during high-risk infusions.
- Early recognition of the signs and symptoms of infiltration and extravasation is critical in limiting exposure to the toxic agent and minimizing soft tissue damage.
- Early implementation of appropriate antidotes, such as hyaluronidase, phentolamine, or sodium thiosulfate, and/or thermal compression, may also minimize tissue damage and accelerate healing.

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