Clinical Pharmacology & Toxicology Pearl of the Week

Extravasation Injuries Part I

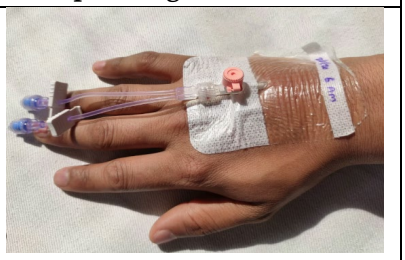
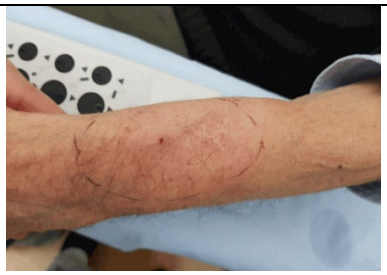
~ Acidic, Alkaline, and Osmotic Vesicants ~

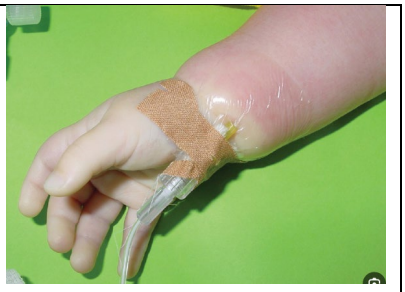
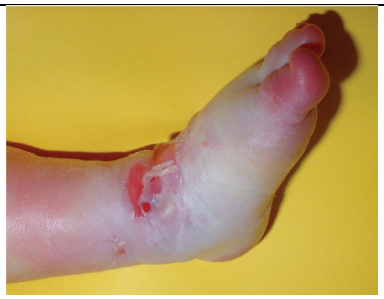
Case:

- ✓ A 76 year old female is brought into the ED after EMS were called for altered mental status.
- ✓ On scene, the patient's blood glucose was noted to be 2.3 mmol/L – therefore, an 18G IV was placed in the patient's right antecubital fossa, and she was provided a total of 50 g of dextrose in the form of two 50 mL ampules of D50 (Dextrose 50%) – administered 20 minutes ago.
- ✓ On arrival to the ED, the patient is more alert, but complaining of significant pain to her IV site – nursing indicates swelling and are concerned for a developing extravasation injury.

Background:

- ✓ Extravasation is leakage or inadvertent administration of a cytotoxic agent (i.e., chemotherapeutic) or vesicant drug/solution (an agent that causes irritation, and classically blistering) into the extravascular space.
- ✓ Initial symptoms include persistent pain, burning, stinging irritation, blanching, erythema at the site; similar to symptoms seen with infiltration of non-vesicants – Vesicant exposure, however, can progress to tissue ischemia, thrombophlebitis, necrosis, and ulceration.
- ✓ Extent of injury is divided by Grades 1-4 as outlined below:

Grade	Description	Example Image
1	- Pain at infusion site - No erythema or blanching - Localized swelling	 The risk of extravasation injuries during iron infusion therapy (osborneslaw.com)
2	- Pain at infusion site - Swelling (up to 25% of extremity above or below site) - **Slight erythema** - Good pulse distally - Brisk cap refill below site <2 sec	 Bolzacchini 2019

3	- Pain at infusion site - Moderate swelling at site (25-50% of extremity above or below site) - **Marked erythema** - **Blanching** - Good pulse distally - Brisk cap refill below site <2 sec - **Skin cool to touch**	 4 – Vascular Access | Anesthesia Key (aneskey.com)
4	- Pain at infusion site - Severe swelling (>50% of extremity above or below site) - Very marked erythema – **extending beyond borders of edema** - Blanching - **Decreased or absent distal pulse** - **Delayed cap refill** - Skin cool to touch - **Skin breakdown, including blistering or necrosis**	 Jöhr 2018

Adapted from Ong 2020; Grading scheme proposed by Heckler 1984

- ✓ Risk factors for inadvertent extravasation include (Ipema 2021; Stefanos 2023):
  - Cannulation technique and line placement (e.g., venous access overlying a joint, provider experience)
  - Poor peripheral vessel integrity and blood flow (e.g., elderly, prior radiotherapy)
  - Limited venous and lymphatic drainage (e.g., obstruction or resection from surgery)
  - Barriers to communicating discomfort / pain
  - Vesicant properties (pH, osmolality, vasoactivity, cytotoxicity)
  - **Pediatrics:** Use of butterfly needles or small catheters which allow blood flow around the catheter

- ✓ Other than extravasation of directly cytotoxic agents and vasopressors: **acidic**, **alkaline**, and **hyper- and hypo-osmolar** agents pose a threat to tissue – examples and their mechanisms are outlined below (Stefanos 2023):

Vesicant Class	**Specific Agents Reported**	**Mechanism**
Acidic	- Amiodarone - Gentamicin - Metronidazole - Nicardipine - Vancomycin - Promethazine - Doxycycline - Conivaptan - Pentamidine - Esmolol	Acidic agents lead to vasoconstriction and tissue edema, as well as cellular desiccation, coagulative necrosis, and ulceration.
Alkaline	- Acyclovir - Ganciclovir - Phenytoin - Phenobarbital - Sodium thiopental	Alkaline agents lead to protein dissolution, collagen destruction, and breakdown of cell membranes – leading to liquefactive necrosis.

Hyper- & Hypo-osmolar	- Radiocontrast material - TPN - Aminophylline - Calcium chloride / gluconate - Dextrose (10-50%) - Mannitol (20%) - Hypertonic Saline - Nafcillin - Potassium chloride - Magnesium sulfate - Arginine - Ampicillin - Sodium bicarbonate - Valproic acid - Propylene glycol containing substances (e.g., diazepam, lorazepam, nitroglycerin, digoxin, phenobarbital, phenytoin)	In general, large osmotic shifts across cell membranes cause direct cell damage, oxidative stress, apoptosis, and inflammation. Hyperosmolar agents may lead to significant fluid accumulation in the tissues, leading to compartment syndrome.

Table adapted from **Stefanos 2023**.

Non-pharmacologic Management

- ✓ Prompt recognition and non-pharmacologic supportive care is critical in the management of extravasation of any cytotoxic or vesicant agents **at the first sign or symptom (**Stefanos 2023; Ong 2020; Lawson 2013):
    1. **STOP the Infusion + DISCONNECT the IV tubing line –** infusion or push should be stopped as soon as the patient describes symptoms <u>or</u> signs of irritation are evident.
    2. **Attempt Vesicant Aspiration –** leave the catheter or needle in place and attempt to aspirate drug and surrounding fluid with 3-5 cc of blood drawn back where possible.
    3. **Elevate the Affected Limb –** to promote lymphatic resorption of the drug, for at least 24-48 hours as able.
        - <u>*Caution:*</u> Limb elevation in suspected compartment syndrome may further worsen tissue ischemia – if compartment syndrome is suspected (pulselessness, pallor, pain out of proportion, elevated CK etc.), seek surgical consultation (Plastic Surgery).
    4. **Apply WARM or COLD Compress –** Currently, there is no head to head comparisons for use of COLD or WARM compresses; for most non-cytotoxic vesicants, WARM compresses are more commonly employed.
        a. <u>Application:</u> 20-60 minutes 3-4 times / day for 24-72 hours.
        b. ***WARM Compresses favored? –*** Preferred for some cytotoxic agents (e.g. vinca alkaloids, epipodophyllotoxins, oxaliplatin), vasopressors, phenytoin, radio-contrast media.
            i. modifies viscosity, increases local blood flow, and may enhance drug removal.
    5. **Consider Surgical Consultation –** debridement and excision of necrotic tissue may be required if pain persists >1-2 weeks, or if clinical concern for compartment syndrome develops.

Pharmacologic Management - *Hyaluronidase*

6. To be considered in Acidic, Alkaline, or Osmotic vesicant extravasation in (Stefanos 2023; Ong 2020):

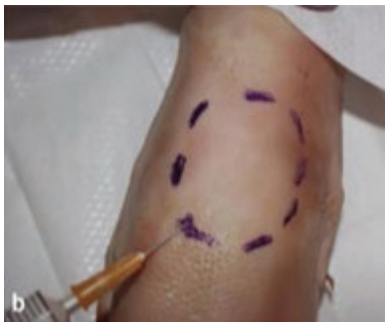
a. Grade 1-2 injuries with no improvement after 30 minutes of non-pharmacologic adjuncts, but ideally before 1-hour post extravasation event.
b. Grade 3-4 injuries alongside non-pharmacologic adjuncts.

7. Hyaluronidase works by hydrolyzing hyaluronic acid – a key component of the extracellular matrix of soft tissue cells.
a. Through this action, it can facilitate improved absorption and dispersion of extravasated agents.

8. Numerous studies have demonstrated the rapid effect of Hyaluronidase for the symptomatic extravasation of the acidic, alkaline, and osmotic agent – effects being seen usually within minutes (Stefanos 2023; Ong 2020; Lawson 2013).

9. The exact timing of when to use Hyaluronidase is uncertain (Ong 2020; Laurie 1984)
a. Extravasation studies using calcium chloride in rabbits demonstrate beneficial effects when Hyaluronidase use was delayed by 1-hour.
b. Early use <30 minutes, and further delays in use beyond 1-hour, showed no statistical significance for improved outcome – however, trended towards benefit.

10. DOSING + ADMINISTRATION (Stefanos 2023; Ong 2020)



Dougherty 2011

a. Dilute 0.1 mL of Hyaluronidase 150 U/mL into 0.9 mL of 0.9% NaCl to create a 15 U/mL solution.
i. Divide the above into 5 tuberculin syringes of 0.2 mL each.
ii. Inject intradermally at 5 points around the periphery of the extravasation site.
b. Repeat dosing may be done q30-60 minutes up to 150 Units.
i. Total doses of 450 Units have been used without adverse effect (Ong 2020).

11. Possible adverse effects of Hyaluronidase infiltration include (Jung 2020):
a. Local irritation / pruritus
b. Allergic reactions (Type I hypersensitivities)
i. Reported as low as 0.05% and 0.69%
c. Delayed hypersensitivity reactions (Type IV)

Case Resolution:

- ✓ You institute the above recommended non-pharmacologic management strategies; however, the patient appears to progress to a Grade 3 injury – she demonstrates no signs of compartment syndrome.

- ✓ You move to the administration of Hyaluronidase after 1-hour and over the next 2 hours, the patient notes significant improvements in pain, swelling, and erythema.

~ Stay Tuned for Extravasation Injuries Part II: Peripheral Vasopressors ~

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK).

References / Resources

- Stefanos SS et al. Management of noncytotoxic extravasation injuries: a focused update on medications, treatment strategies, and peripheral administration of vasopressors and hypertonic saline. *Pharmacotherapy*. 2023;43(4):321-37.
- Ong J et al. Recommendations for management of noncytotoxic vesicant extravasations. *J Infus Nurs.* 2020;43(6):319-43.
- Ipema H et al. What are current recommendations for treatment of drug extravasation? *University of Illinois Chicago: Drug Information Group*. Published online February 2021. Link: What are current recommendations for treatment of drug extravasation? | Drug Information Group | University of Illinois Chicago (uic.edu)
- Laurie SW et al. Intravenous extravasation injuries: the effectiveness of hyaluronidase in their treatment. *Ann Plast Surg*. 1984;13(3):191-4.
- Heckler FR. Current thought on extravasation injuries. *Clinics Plast Surg*. 1989;16:557-63.
- Bolzacchini E et al. First report of pembrolizumab extravasation. *Hematol Med Oncol*. 2019;5:1-2.
- Jöhr M. Extravasation. In: *Managing Complications in Paediatric Anaesthesia.* Cambridge: Cambridge University Press. 2018:94-96. doi:10.1017/9781316823064.030
- Dougherty L et al. Advanced practice in the management of extravasation. *Cancer Nurs Prac.* 2011;10(5):16-22.
- Lawson AL et al. Identification of highly concentrated dextrose solution (50% dextrose) extravasation and treatment – a clinical report. *Am J Emerg Med.* 2013;31:886.e3-e5.
- Jung H. Hyaluronidase: an overview of its properties, applications, and side effects. *Arch Plast Surg*. 2020;47:297-300.