Clinical Pharmacology & Toxicology Pearl of the Week

Extravasation Injuries Part II

~ Peripheral Vasopressors ~

Case:

- ✓ A 67 yo male arrives to the ED with fever, tachycardia, and hypotension. Workup reveals findings concerning for possible urosepsis.

- ✓ The patient receives early broad-spectrum antibiotics as well as 4L of IV ringers lactate – despite this remains hypotensive. A decision is made to begin peripherally administered Norepinephrine

- ✓ 1 hour after initiation of Norepinephrine at an antecubital site, the patient begins to demonstrate swelling, blanching, and excessive pain to the site of infusion – in addition, their hypotension returns; Nursing is concerned of a potential extravasation of Norepinephrine.

Background:

- ✓ *Please refer to CPT Pearl "Extravasation Injuries Part I" for a discussion on the concept of extravasation injuries, clinical symptoms, and grading.*

- ✓ Vasopressors carry risk of tissue injury in peripheral extravasation given their vasoconstrictive effects which can result in local tissue ischemia and resultant necrosis.

- ✓ Given concerns over tissue damage potential, vasopressor use had historically required the placement of central venous access for administration – a process which takes time, carries risks, and requires extra-training.

- ✓ Early administration of vasopressors (especially in the setting of sepsis and septic shock) carries morbidity and mortality benefits.
    - Current sepsis guidelines therefore recommend prioritizing treatment of a low mean arterial pressure (MAP) with the use of <u>peripherally</u> administered vasopressors.

- ✓ Recent meta-analysis by Owen et al. (2021), which included 23 studies and over 16,000 patients (mixture of adults and children) found that the pooled incidence of adverse local anatomic events (i.e. extravasation) was 1.8% among adults and 3.3% among children – furthermore, 19/23 studies reported either no adverse events or only mild local reactions.
    - Only 4 studies reported severe reactions, such as ischemia and skin necrosis.
    - Studies varied on their management of extravasation events.

- ✓ Despite a low incidence in the literature, prevention, early recognition, and active management can help to avoid the potentially detrimental effects of vasopressor extravasation – especially where peripheral use is becoming more common.

Prevention

- ✓ Placement of more proximal IV access may lessen the risk of extravasation injury.
    - A 2015 meta-analysis (Loubani 2021) found that extravasation events were more likely when IV placement was below the level of the antecubital fossa.
    - In contrast, Owen et al, (2021) found that the incidence did not differ significantly according to vasopressor type, catheter location, nor catheter gauge.

- ✓ Use of peripheral vasopressors should be at the lowest effective concentration and for ideally <24 hours before transition to central access use.
    - Although this is incorporated into numerous hospital policies, it is based on scant and extremely variable evidence.
        - Meta-analysis by Loubani et al. (2015) – average time to extravasation 35.2 hours (Range of 0.25-240 hours), with the large majority occurring after 24 hours.
        - Lewis et al. (2019) – median of 21 hours (Range of 8-43 hours)
        - Meta-analysis by Owen et al. (2021) – 10 adult studies reported a range of 1.3-49 hours, with 5 studies reporting an average of 12-24 hours.

- ✓ Articles highlight vigilant monitoring and early recognition of potential extravasation events as key in preventing morbidity.
    - A CMAJ review by Araiza et al. (2022) recommends assessment of the site of peripheral vasopressor use every 30-60 minutes. If extravasation is recognized, the following management is recommended (*see below*)

Non-pharmacologic Management

- ✓ Prompt recognition and non-pharmacologic supportive care is critical in the management of all extravasations, including vasopressors **(**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 or signs of irritation are evident.
    2. **If still required, ensure vasopressor infusion is restarted via a new/secure access site**
    3. **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.
    4. **Elevate the Affected Limb** – to promote lymphatic resorption of the drug, for at least 24-48 hours as able.
        - *Caution:* 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).
    5. **Apply WARM Compress (avoid COLD)** – promotes vasodilation and drug resorption
        - Application: 20-60 minutes 3-4 times / day for 24-72 hours.
    6. **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

- ✓ Consider addition of pharmacologic adjuncts for:
  - Grade 1-2 injuries with no improvement after 30 minutes of non-pharmacologic adjuncts.
  - Grade 3-4 injuries alongside non-pharmacologic adjuncts.

- ✓ <u>FIRST LINE</u>: *Phentolamine*
  - Promotes vasodilation through reversible alpha(1)-antagonism helping to reverse the vasoconstrictive effects carried by most vasopressors medications.
  - Touted as a first-line agent for most vasopressors; early administration, especially within 12 hours of extravasation demonstrates increased efficacy (Reynolds 2014)
  - **DOSING:** 0.1-0.2 mg/kg (5-10 mg) Phentolamine diluted in 10 mL of 0.9% sodium chloride
    - *<u>SPECIAL SCENARIO</u>*: *Digital Injection of Epinephrine (i.e. Auto-injector Epi-Pen)*
      - Dilute 0.5-4.5 mg in 5 mL of 0.9% sodium chloride and inject SQ along edge of finger.
  - **ADMIN:** Inject total 10 mL solution in 2 mL S! aliquots around the site of extravasation (swelling / blanching edge)
    - Stefanos 2023 recommends initial 10 mL to be injected through the remaining interstitial catheter if available.
    - May repeat additional dose in 60 minutes if ongoing signs of blanching, ischemia, pain etc.
    - Further repeat doses warrant discussion with Plastic Surgery.
  - **ADVERSE EVENTS:**
    - Monitor for hypotension and reflex tachycardia.

- ✓ <u>SECOND LINE</u>: *Terbutaline*
  - A Beta(2)-agonist that causes vasodilation, counteracting the vasoconstrictive effects of vasopressors.
  - In instances where phentolamine is inaccessible, appropriate as a second-line therapy.
  - **DOSING:** 1 mg Terbutaline in 10 mL of 0.9% sodium chloride
  - **ADMIN:** *As per Phentolamine*
    - May repeat dose in 30-60 minutes if ongoing signs of blanching, ischemia, pain etc.
    - Further repeat doses warrant discussion with Plastic Surgery.
  - **ADVERSE EVENTS:**
    - Monitor for hypotension and reflex tachycardia
    - Contraindicated in children <= 2 years old and neonates, due to prolonged half life (2.9 hours) and risk of systemic effects.

- ✓ <u>THIRD LINE / Adjunct:</u> *Topical Nitroglycerin 2% Ointment*
    - Arteriovenous vasodilatory properties that have been used as monotherapy or as an adjunct to Phentolamine and Terbutaline use.
    - Potentially FIRST LINE for:
        - Methylene Blue (Ong 2020; Reynolds 2014)
        - Vasopressin (Ong 2020; Reynolds 2014)
    - **DOSING/ADMIN:** Apply 4mm/kg (up to 1 inch) to affected area
        - Monitor BP q15 minutes x 5, given likelihood of some systemic absorption precipitating hypotension.
        - Use on broken skin may alter absorption, efficacy, and safety – avoid this.
        - May repeat in 8 hours if no resolution.
    - **ADVERSE EVENTS:**
        - As above re: hypotension monitoring.

Case Resolution:

- ✓ You recognize that the patient has what appears to be a Grade 3 extravasation injury secondary to Norepinephrine.

- ✓ You institute appropriate nonpharmacologic management, including obtaining a new, proximal peripheral IV access site for continued vasopressor administration.

- ✓ Given the grade of extravasation, you elect to administer SQ Phentolamine which results in rapid resolution of the patient's pain, blanching and erythema – you also discuss with Plastic Surgery who have agreed to see the patient.

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.
- Araiza A et al. Administration of vasopressors through peripheral venous catheters. *CMAJ*. 2022;194:e739.
- Evans L et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock. *Intensive Care Med*. 2021;47:1181-247.
- Loubani OM et al. 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;30:653.e9-17.
- Owen VS et al. Adverse events associated with administration of vasopressor medications through a peripheral intravenous catheter: a systematic review and meta-analysis. *Crit Care*. 2021;25:146.
- Lewis T et al. Safety of the peripheral administration of vasopressor agents. *J Intensive Care Med*. 2019;34(1):26-33.
- Reynolds PM et al. Management of extravasation injuries: a focused evaluation of noncytotoxic medications. *Pharmacotherapy*. 2014;34(6):617-32.

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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). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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