Clinical Pharmacology & Toxicology Pearl of the Week

~ Drug-Induced Edema ~

Drug-induced edema is caused by many drugs & can coincide with or worsen pre-existing peripheral edema

Tissue edema develops due to one or more of the following:

- Increased vascular permeability
- Increased hydrostatic pressure
- Decreased oncotic pressure in the blood vessels

Drugs that directly or indirectly upset the balance between hydrostatic and oncotic pressures (Figure 1) or that alter vascular permeability have the potential to cause tissue edema.

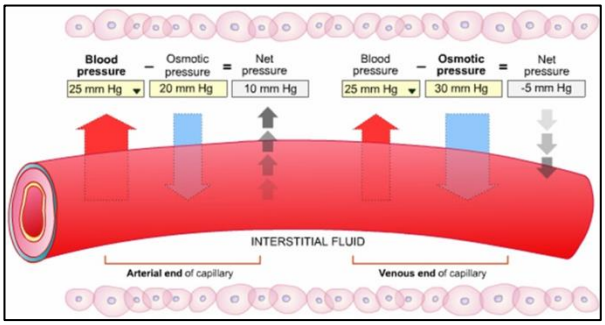

Figure 1: Arterial & Venous Pressure Gradients

Drug-related changes to hydrostatic pressure occur via ↑ blood pressure (BP) &/or ↑ blood volume (BV; either ↑ total body volume via $Na^+ + H_2O$ retention or ↑ blood pooling via vaso/venodilation)

Drug-induced alteration to vascular permeability can occur via numerous mechanisms, some of which include:

- Bradykinin (has a very potent effect on blood vessels, leading to ↑↑ vascular permeability)
- Histamine release from mast cells
- Increased nitric oxide release
- Activation of the complement cascade

Table 1: Drugs implicated in causing peripheral edema

Common Culprit Drugs		Edema Mechanism	Pharmacologic/Physiologic Mechanism
Non-DHP CCBs:	amlodipine, nifedipine	↑ hydrostatic pressure	Precapillary vasodilation via L-type calcium channels
Neuropathic pain agents:	gabapentin, pregabalin	↑ hydrostatic pressure	Precapillary vasodilation via L-type calcium channels
Non-Steroidal Anti-Inflammatories:	buprofen, ketorolac, naproxen	↑ BV & BP	Decreased GFR via inhibition of prostaglandins --> activation of renin angiotensin aldosterone system (RAAS) , sodium & water retention
ACE inhibitors:	ramipril, perindopril, enalapril etc.	↑ vascular permeability	Decreased degradation of bradykinin
Dopamine agonists:	pramipexole, ropinirole	Hypothesis is ↑ BV	? via activation of RAAS system
Insulin		↑ BV	Activation of sodium channels in the distal nephron (mineralocorticoid-like activity)
Nitrates		↑ venous hydrostatic P	Potent venodilation via Nitric Oxide & cGMP --> blood pooling
Steroids:	glucocorticoids, mineralocorticoids, estrogen, testosterone	↑ BV & BP	RAAS activation, mineralocorticoid receptor activation --> sodium & water rentention
Antipsychotics:	quetiapine, olanzapine, clozapine	Hypothesis is ?compensatory ↑ BV	many have alpha-1 antagonist properties --> orthostasis, activation of RAAS --> sodium & water retention

Management involves deciding whether the edema is severe or life-threatening (ie: ACE-inhibitor angioedema), in which case the drug should be discontinued immediately

If it is not severe/life threatening, then depending on the mechanism of edema, options include stopping/switching the medication, using diuretics, RAAS-blocking agents (beta blockers, ACEi or ARBs) & compression stockings to control the edema

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.