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.

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 (describe what happens with bradykinin that vascular permeability is affected)
- 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:	ibuprofen, 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 venodilatation via Nitric Oxide & cGMP → blood pooling
Steroids:	glucocorticoids, mineralocorticoids, estrogen, testosterone	↑ BV & BP	RAAS activation, mineralocorticoid receptor activation → sodium & water retention
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 (beware of the prescribing cascade if doing so), RAAS-blocking agents (beta blockers, ACEi or ARBs) & compression stockings to control the edema.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

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.

More CPT Pearls of the Week can be found HERE.

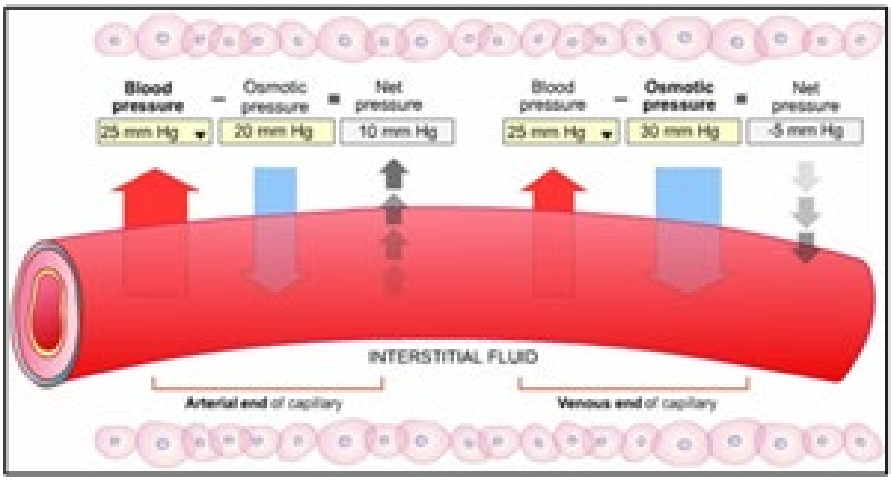

Figure 1 : Arterial & Venous Pressure Gradients

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