Clinical Pharmacology & Toxicology Pearl of the Week

~ Colchicine ~

- ✓ Colchicine is a plant alkaloid isolated from the Autumn Crocus and Glory Lily flowers
- ✓ Used in Gout, Pseudogout, Behcet's disease, Pericarditis, Familial Mediterranean Fever, idiopathic vasculitis and Sweet syndrome
- ✓ It exerts anti-inflammatory effects by inhibiting leucocyte function & recruitment
- ✓ **Pharmacokinetics**
  - Colchicine's pharmacokinetics contribute to its narrow therapeutic window:
  - Absorption: well absorbed orally, efflux from enterocytes and hepatocytes via P-Glycoprotein (P-GP)
  - Distribution: very lipophilic, distributes rapidly into all major organ systems
  - Metabolism: high first-pass metabolism, primarily by liver CYP3A4
  - Elimination: 40-65% renal excretion as unchanged drug; enterohepatic & biliary clearance
- ✓ **Pathophysiology and Toxicity**
  - Colchicine binds to several sites on cell microtubules and inhibits proper function, leading to inhibition of mitosis (cell division) in the metaphase stage. This leads to cellular dysfunction and death
  - Historically, the toxic dose was reported to be 0.8 mg/kg. However, ingestions of 0.5 mg/kg and lower have resulted in fatalities and reported ingestions greater than 0.8 mg/kg have survived. The inability to properly quantify the toxic dose in humans is due in part to inaccuracies in reported dose ingestion by patients
  - Colchicine toxicity may occur in the setting of:
    - Concurrent use of CYP3A4 inhibitors: protease inhibitors, imidazoles, clarithromycin, grapefruit juice
    - Administration of P-GP inhibitors: clarithromycin, tacrolimus, cyclosporine
    - Renal and/or liver impairment
    - Co-prescription of statin medications, specifically: pravastatin, fluvastatin, lovastatin
    - Overdose (intentional vs. unintentional) or ingestion of the Autumn Crocus or Glory Lily

Table 1: Phases of Colchicine Toxicity

Early Phase (0-24h)	Multi-organ failure Phase (1-7 days)		Recovery Phase (7-21 days)
Nausea Vomiting Diarrhea Abdominal pain Dehydration	Respiratory:	Respiratory Distress Syndrome	Recovery of organ failure(s) Leukocytosis Alopecia Neuropathy Myopathy
	Cardiovascular:	Congestive heart failure Cardiac arrhythmia, cardiac arrest	
	Neurologic:	Seizures Encephalopathy Cerebral edema Neuropathy, myopathy	
	Hematologic:	Cytopenias Bone marrow suppression Hemolysis, DIC	
	Metabolic:	Metabolic acidosis HypoK, hypoNa, hypoP04, hypoglycemia/hyperglycemia	
	Other:	Renal failure, Liver failure Immune compromise & Sepsis	

- ✓ **Treatment may involve the following:**
  - ED observation for at least 8-12 hours if asymptomatic. Admit for at least 24 hours if symptomatic
  - Aggressive GI decontamination
    - may include gastric lavage, single dose activated charcoal
  - Multi-dose activated charcoal to interrupt enterohepatic recirculation
  - IV fluids
  - Antibiotics if infection suspected
  - Dialysis if AKI is present
  - G-CSF if neutropenia

The Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. 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).