Clinical Pharmacology & Toxicology Pearl of the Week

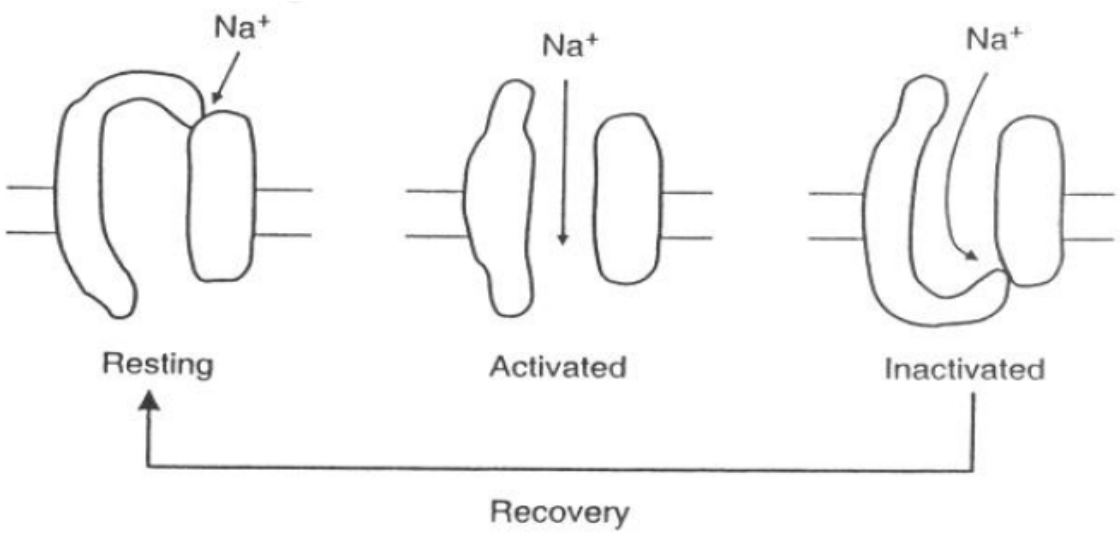
~ Phenytoin, Part 1 ~

Case:

- ✓ A 60-year-old male with a known seizure disorder ingested 90 of his 100 mg phenytoin pills at 1300 hours.
- ✓ The patient is comatose with stable vitals. No cardiac toxicity is observed. A phenytoin concentration 8 hours post-ingestion was 190 umol/L (N = 40-80).
- ✓ What is the role of activated charcoal and extracorporeal removal versus supportive care in the management of phenytoin toxicity?

Background:

- ✓ Hydantoins inhibit sodium channels by reducing their capacity for recovery after inactivation
- ✓ Delay activation of outward potassium current and prolong the neuronal refractory period
- ✓ May also inhibit reuptake of adenosine → inhibit excitatory neurotransmitter release
- ✓ Because they bind preferentially to the inactivated and resting state, and are "fast on fast off", cardiac sodium channel blockade features are usually not seen after oral overdose



(Kolecki and Curry, 1997)

Risk factors for phenytoin toxicity:

- ✓ Mutations in CYP enzymes responsible for phenytoin metabolism (especially 2C9 and 2C19)
- ✓ Coingestants that:
  - inhibit CYP enzymes responsible for phenytoin metabolism
  - displace phenytoin from binding sites

- ✓ Hypoalbuminemia
- ✓ Chronic renal failure

Typical clinical features of phenytoin toxicity:

- ✓ Mild: nystagmus
- ✓ Moderate: nystagmus, slurred speech, nausea, vomiting, ataxia, confusion
- ✓ Severe: coma, movement disorders, respiratory depression
- ✓ IV phenytoin toxicity may also present with hypotension and dysrhythmias if given too quickly. This is from the diluent (propylene glycol) rather than the phenytoin itself.

Atypical clinical features of phenytoin toxicity:

- ✓ Choreoathetosis
- ✓ Dystonia
- ✓ Orofacial dyskinesias
- ✓ Asterixis
- ✓ Encephalopathy
- ✓ These are due to alterations in dopaminergic, cholinergic and serotonergic activity
- ✓ Risk factors for atypical phenytoin toxicity:
  - History of neuropsychiatric disease
    - especially reduced impulse control (ADHD, OCD, disruptive behavior)
  - Age < 40
  - Already on multiple anticonvulsants or antipsychotic
  - Structural brain lesion (especially basal ganglia)
  - Prior dyskinesias
  - Higher [phenytoin], especially after single IV infusion
- ✓ Symptoms may resolve with discontinuation of drug
  - May persist for months to several years, long after the drug has been DC' d

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).