Clinical Pharmacology & Toxicology Pearl of the Week

~ Phenytoin, Part 2 ~

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?

Management:

- ✓ Attention to airway, breathing, and circulation is paramount if the patient has altered LOC.
- ✓ Cardiac toxicity and seizures are extremely unlikely after phenytoin overdose. Their presence should prompt a consideration of other etiologies rather than attributing them to phenytoin first.
- ✓ Phenytoin binds to activated charcoal
    - Single dose activated charcoal can be administered after acute ingestions if there are no contraindications
    - Multi-dose activated charcoal can be considered for substances that undergo enterohepatic recirculation, such as phenytoin. However, it has not been shown to improve outcome or shorten hospital stay after phenytoin overdose
- ✓ Extracorporeal removal of drugs can be considered when the drug meets several of the following properties: low molecular weight, low protein binding, high water solubility, low volume of distribution (< 1 L/kg), and low endogenous clearance (<4 ml/kg/min).
- ✓ At therapeutic concentrations, the apparent elimination half-life is approximately 22 (range, 7-42) hours.
- ✓ In overdose, the apparent elimination half-life increases; in one case, it was reported to be as long as 103 hours. This explains why massive phenytoin ingestions may to prolonged toxicity and extended hospital stays.
- ✓ Although phenytoin is highly protein bound at therapeutic doses, the free fraction increases after overdose. The properties of phenytoin are below (Anseeuw et al, 2015):

Box 1. Physicochemical and Pharmacokinetic Properties of Phenytoin

Molecular mass: 252 Da
Oral bioavailability: 90%
Protein binding: 90% (70%-80% in hypoalbuminemia)
Volume of distribution: 0.6-0.8 L/kg
Therapeutic range[a]: 10-20 µg/mL (39.6-79.2 µmol/L)
Toxic ingestion: ≥20 mg/kg
Toxic plasma concentrations: ≥20 µg/mL (≥79 µmol/L)

[a]To convert units, 1.0 µg/mL = 3.96 µmol/L.

- ✓ A summary of the recommendations from the EXTRIP workgroup on extracorporeal removal of phenytoin after overdose is as follows (Anseeuw et al, 2015):

Box 2. Executive Summary of Recommendations

General statement regarding use of ECTR

1: ECTR would be reasonable in selected cases of severe phenytoin poisoning. (*3D*)

Indications for ECTR

2.1: ECTR is suggested if prolonged coma is present or expected. (*2D*)

2.2: ECTR would be reasonable if prolonged incapacitating ataxia is present or expected. (*3D*)

2.3: We recommend *not* to perform ECTR solely based on suspected dose of phenytoin ingested. (*1D*)

2.4: We recommend *not* to perform ECTR solely based on serum phenytoin concentration. (*1D*)

Cessation of ECTR

3: ECTR should be discontinued when clinical improvement is apparent. (*1D*)

Choice of ECTR

4.1: Intermittent hemodialysis is the preferred ECTR in phenytoin poisoning. (*1D*)

4.2: Intermittent hemoperfusion is an acceptable alternative if intermittent hemodialysis is not available. (*1D*)

Abbreviation: ECTR, extracorporeal treatment.

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).