Clinical Pharmacology & Toxicology Pearl of the Week

~ Extracorporeal Removal of Drugs and Toxins ~

Case:

- ✓ A 32-year-old male ingests 250 ml of gas line antifreeze (95% methanol) in a suicide attempt.
- ✓ A methanol concentration performed 4 hours after ingestion is 80 mmol/L.
- ✓ The patient has no evidence of metabolic acidosis and no decreased vision.
- ✓ Nephrology is consulted and they agree to dialyze the patient after reviewing the EXTRIP guidelines (METHANOL | extrip-workgroup).
- ✓ The patient is started on fomepizole, dialyzed for 10 hours, and makes a full recovery.

Properties of drugs amenable to extracorporeal removal (e.g., hemodialysis):

1. Low molecular weight

- ✓ Historically, a molecular weight of 500 Daltons (Da) was the cutoff used to determine if a molecule was too large to pass through older dialysis membranes.
- ✓ Use of high-flux and high-efficiency dialysis membranes is now standard practice in dialysis centers. They have higher molecular cutoff values (10,000 Da vs 500 Da), larger surface areas, and enhanced ultrafiltration coefficients as compared with older membranes.

2. Low volume of distribution (Vd)

- ✓ Vd refers to the theoretical space into which 100% of an administered drug would distribute.
- ✓ It is calculated as: Vd = amount of drug in body / plasma drug concentration.
- ✓ In general, drugs with a high lipid solubility, low rates of ionization, or low plasma protein binding have higher volumes of distribution than drugs which are more polar, highly ionized, or high plasma protein binding. As an example, amiodarone has a Vd of 250 L/kg.
- ✓ A Vd of < 1 L/kg has historically been used as a number below which the drug may be amenable to removal by dialysis.

3. Low protein binding

- ✓ Because the protein–poison complex is characteristically bigger than pore size, poisons that are highly protein bound are not considered dialyzable.

- ✓ In poisoning, protein binding sites become saturated, increasing the proportion of free, and therefore dialyzable, poison.

- ✓ This explains the high removal rate of protein-bound drugs (such as valproate and salicylate) that is achieved in actual poisoning.

4. High water solubility

- ✓ A drug that is highly water soluble (and therefore has low fat solubility) is less likely to leave the vascular space and is therefore more amenable to extracorporeal removal.

5. Low endogenous clearance

- ✓ Dialysis should also be considered if the amount of poison dialyzed constitutes a significant addition to the normal body mechanisms.

- ✓ Extracorporeal clearance must represent at least 30% of total clearance to be a significant contributor to drug removal.

- ✓ Therefore, drugs like ethanol and cocaine (which have high endogenous clearance because of enzyme metabolism) are not dialyzed, whereas drugs like methanol (which has an elimination half-life of 40-55 hours when fomepizole or ethanol are given) are more amenable to dialysis.

Some dialyzable drugs and toxins:

Drug	**Molecular wt. (Daltons)**	**Vd (L/kg)**	**Protein binding (%)**	**Water solubility**	**Endogenous clearance (ml/min/kg)**
Salicylate	138	0.2	50	Yes	0.9
Methanol	32	0.6	0	Yes	0.7
Ethylene Glycol	62	0.6	0	Yes	2.0
Lithium	7	0.6	0	Yes	0.4
Theophylline	180	0.5	56	Yes	0.7
Valproate	144	0.2	90	Yes	0.1
Acetaminophen	151.2	0.8-1.0	10-30	Yes	~ 5.0

References:

1. extrip-workgroup.org

2. Blood Purification in Toxicology: Nephrology's Ugly Duckling. Marc Ghannoum, Thomas D. Nolin, Valery Lavergne, and Robert S. Hoffman for the EXTRIP workgroup. Advances in Chronic Kidney Disease, Vol 18, No 3 (May), 2011: pp 160-166.

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.

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