Clinical Pharmacology & Toxicology Pearl of the Week

~ Introduction to Pharmacokinetics ~

- ✓ Pharmacokinetics can be simplified as "What the body does to the drug"
- ✓ It consists of four basic concepts: Absorption, Distribution, Metabolism, and Elimination
- ✓ Understanding pharmacokinetics can help improve medication prescribing and delivery, and help to trouble shoot when drugs are not behaving as expected

Absorption

- ✓ Xenobiotics (ie: any foreign chemical compound) can be absorbed via the GI tract, mucosal surfaces, transdermally, from subcutaneous and intramuscular depots, or transcutaneously
- ✓ Factors that determine xenobiotic absorption are listed in Table 1
- ✓ For gastrointestinal absorption:
  - Pills must disintegrate and dissolve into solution prior to absorption
  - Acidic compounds are more easily absorbed in the acidic stomach as they will be uncharged
  - Basic compounds are more easily absorbed in the alkaline small intestine as they will be uncharged
  - **More importantly:** the massive surface area of the small intestines, due to the microvilli, translates to most xenobiotics being absorbed there, regardless of being an acid or a base
    - Xenobiotics or conditions that <u>delay gastric emptying will typically delay absorption</u> of other xenobiotics Ex: Antimuscarinic medications, Salicylates, ETOH, Opioids, Diabetic gastroparesis
    - Xenobiotics or conditions that <u>enhance gastrointestinal transit time will decrease absorption</u> of other xenobiotics Ex: Whole Bowel Irrigation, Short Gut Syndrome
- ✓ Blood draining from the GI system travels to the liver and undergoes <u>first pass metabolism</u>. This decreases the amount of xenobiotic seen in systemic circulation. As such, <u>it decreases the amount of xenobiotic absorbed.</u>
- ✓ Bioavailability is the percent of a xenobiotic given to a patient that is found intact in systemic circulation.
  - It is reduced by decreased absorption in the gut, metabolism by gut microbiota, destruction from stomach acid or gut digestive enzymes, and first pass metabolism
  - In overdose, pre-systemic metabolism is often saturated resulting in a higher bioavailability

<u>Table 1: Factors determining xenobiotic ability to cross membranes</u>

- Polarity
- Charge/Ionization
- Molecular size
- Concentration Gradient
- Surface area of membrane
- pH of solution on either side (affects ionization)
- Active Transporter Proteins / Efflux Proteins
- Lipophilicity

<u>Bioavailability of different delivery methods</u>

- IV: 100%
- SC: 75-100%
- IM: 75-100%
- PO: 5-100%

Distribution

- ✓ After absorption into systemic circulation, xenobiotics distribute into various tissues in the body based on factors outlined in Table 1
- ✓ The volume of distribution (Vd) is a conceptual representation of the theoretical volume within which a xenobiotic distributes in the body.

- ✓ A large Vd (>2L/Kg) represents a drug that distributes significantly into tissues Ex: Digoxin – Vd 5-7 L/Kg
- ✓ A small Vd (<2L/Kg) represents a drug that remains markedly within circulating blood volume Ex: Methanol – Vd 0.77 L/Kg
- ✓ A xenobiotic can only have its clinical effect once it has distributed into the target tissue
  - Example: IV Digoxin will quickly increase plasma digoxin levels, but clinical effect only occurs once it has distributed into cardiac tissue (resulting in a decrease in plasma digoxin levels)
- ✓ An estimation of drug levels assuming 100% absorption can be made using the following equation:

$$\text{Concentration (mg/L)} = \text{Dose} / \text{Vd (L/kg)} \times \text{weight (kg)}$$

Metabolism

- ✓ Xenobiotics undergo metabolism in the body, primarily the liver, to aid in clearance by making them more water soluble for renal or biliary elimination
  - Some xenobiotics are inactive until metabolized to the active compound
  - Some xenobiotics have active metabolites with different half-lives and activity from the parent compound
- ✓ In general, there are two types of metabolic reactions
  - A) Phase 1 reactions: Introduce polar groups to non-polar compounds to allow for phase 2 reactions and improve water solubility
    - Performed by Cytochrome P450 (CYP) enzymes primarily in the liver
  - B) Phase 2 reactions: Conjugate a polar group on a xenobiotic to a more water-soluble moiety, making the compound much more water soluble
    - Primarily occurs in the liver. Examples: Glucuronidation, Sulfonation, or acetylation
- ✓ A small number of xenobiotics are broken down through other systems found in the blood, kidneys, and lung
- ✓ A small number of xenobiotics do not undergo any metabolism

Elimination

- ✓ Xenobiotics are primarily cleared in the urine, or in the feces by biliary secretion
- ✓ Elimination of a xenobiotic depends on factors in Table 1
  - Xenobiotics cleared in the urine also depend on renal perfusion and glomerular filtration rate
  - Xenobiotics cleared in the feces also depend on gut microbiota metabolism and gastrointestinal reabsorption rate
- ✓ When elimination is equal to absorption, a steady state is reached.
  - Typically occurs within four to five half-lives

References:

1. Lewis S. Nelson et al, Goldfrank's Toxicologic Emergencies. 11th ed. New York: McGraw Hill Medical; 2019
2. Buxton IO. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e New York, NY.

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.

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Created: December 18, 2019

Reviewed: February 28, 2025