Clinical Pharmacology & Toxicology Pearl of the Week

Toxicokinetics ≠ Pharmacokinetics Series
Part 1 - Absorption

Pharmacokinetics refers to what the body does to the drug (absorption, distribution, metabolism, elimination).

Pharmacokinetic studies are often conducted during drug development using therapeutic doses.

Pharmacokinetic parameters can often change markedly in the overdose situation, hence the term toxicokinetics.

This series of "toxicokinetics ≠ pharmacokinetics" pearls will focus on key differences between toxicokinetic and pharmacokinetics using cases to illustrate the important points.

Part 1 of this series focuses on differences in absorption.

Case 1:
A 25-year-old female presents to emergency department following an overdose of salicylate. The patient appears well and has no signs of salicylate toxicity. The initial salicylate concentration 4-hours post ingestion is 1.4 mmol/L (therapeutic level 0-.7-1.8 mmol/L).

Repeat salicylate concentration at 8 hours post ingestion was 1.7 mmol/L. At 10 hours it was 1.8 mmol/L, 13 hours = 1.77 mmol/L, and at 18 hours = 1.54 mmol/L.

Is this patient medically cleared?

Case 1 resolution:
The patient was deemed medically cleared after the 18hr salicylate concentration and was admitted to psychiatry. 20 hours after admission (~38 hours post ingestion), the patient developed tinnitus and some mild confusion. Repeat salicylate concentration was 4.9 mmol/L. The patient was treated with urinary alkalinization without dialysis and made a full recovery.

Key points:

- ✓ Therapeutic dose of salicylate reaches peak plasma concentration in about 1 hour. In overdose, salicylate can form bezoars/concretions, cause gastric irritation and pylorospasm resulting in delayed absorption and may not peak until up to 35 hours post ingestion (Rivera et al., 2004)
- ✓ Salicylate is a classic example of a drug that can have erratic absorption kinetics in overdose. Other drugs that can form bezoars include anticholinergics, barbiturates, bromides, other enteric coated tablets, iron, meprobamate, methaqualone, opioids, phenytoin, and verapamil.

Pearl: Overdose can result in delayed peak concentration compared to therapeutic time to peak concentration especially for drugs that tend to form bezoars. It is important to serially monitor drug concentrations to establish a peak and a decline, and correlate them with other relevant labs and clinical status.

Case 2:
A 33-year-old male presents to emergency department two hours after overdose of Tylenol#3. The patient appears well with normal vital signs and no signs of an opioid toxidrome. Four-hour acetaminophen concentration is below treatment threshold at 780 μmol/L. The other labs including transaminases, creatinine, and INR are unremarkable. Is this patient medically cleared?

Case 2 resolution:
Repeat serum acetaminophen concentration done at 7.5 hrs post ingestion was 670 μmol/L, which crosses the nomogram treatment line. Patient was treated with NAC and did not develop any hepatotoxicity.

Key Points:

- ✓ Acetaminophen nomogram "line crossing" refers to an initial acetaminophen concentration below the treatment line at 4 hours, with a subsequent concentration above treatment line.
- ✓ This phenomenon can occur if co-ingestants that slow gastrointestinal motility (anticholinergics, opioids, NSAIDS, salicylates) or modified release acetaminophen formulation (such as Tylenol arthritis®) are involved.
- ✓ If 4-hour [APAP] is non-toxic, repeat the [APAP] 2 hours later. If the repeat [APAP] is higher than the initial 4-hour concentration, a third repeat level 2 hours later should be sent. Treat with NAC if any [APAP] is above the nomogram treatment line.

Pearl: Modified release formulations or co-ingestion of drugs that slow gastrointestinal motility can result in delayed peaks. The same principle applies to other toxins such as antidepressants (e.g., bupropion SR requires observation times of 12-24 hrs for delayed seizures), beta blockers (e.g., metoprolol extended release requires observation times of ~12-13 hrs compared to 6 hours for metoprolol immediate release), and many other toxins.

Other key differences in absorption between toxicokinetics vs. pharmacokinetics:

- ✓ Decontamination strategies can decrease absorption.
  - Examples: charcoal can decrease the amount of drug available for absorption. Whole bowel irrigation can decrease gastrointestinal transit time and potentially decrease absorption.
- ✓ Absorption of certain drugs can be saturable in overdose compared to therapeutic dose.
  - Example: absorption for methotrexate at oral dose of 30mg/m2 is 90%; whereas at oral doses greater than 80mg/m2, absorption for methotrexate is less than 10-20%.
- ✓ Drug-drug interactions in polypharmacy overdose can affect absorption.
  - Example: loperamide (an opioid used in diarrhea treatment) has little psychoactive effect in therapeutic use due to poor absorption and active efflux from CNS by p-glycoprotein. Large overdoses of loperamide or co-ingestion with p-glycoprotein inhibitors (such as quinine) can increase GI absorption and CNS concentration. These strategies are often used in recreational use of loperamide for its euphoric properties.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues with which the CP service can assist.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

References:

- ACMT Toxicology Board Review Course 2020.
- Goodman & Gilman The Pharmacological Basis of Therapeutics, Thirteenth Edition
- Goldfrank's Toxicologic Emergencies, Eleventh Edition.
- Welling PG. Toxicol Pathol. 1995 Mar-Apr;23(2):143-7.
- Kirschner RI, Rozier CM, Smith LM, Jacobitz KL. Nomogram line crossing after acetaminophen combination product overdose. Clin Toxicol (Phila). 2016;54(1):40-6.
- Rivera W, et al. Delayed salicylate toxicity at 35 hours without early manifestations following a single salicylate ingestion. Ann Pharmacother. 2004 Jul-Aug;38(7-8):1186-8.
- Antoniou, T., & Juurlink, D. N. (2017). Loperamide abuse. Canadian Medical Association Journal, 189(23), E803 LP-E803. https://doi.org/10.1503/cmaj.161421