Clinical Pharmacology & Toxicology Pearl of the Week

Part 2 - Toxicokinetics ≠ pharmacokinetics series: Distribution

Pharmacokinetics refers to what the body does to the drug (absorption, distribution, metabolism, elimination). Pharmacokinetic studies are often conducted during drug development using therapeutic dose. Pharmacokinetic parameters can often change markedly in overdose (toxicokinetics). This series of "toxicokinetics ≠ pharmacokinetics" pearls will focus on key differences between toxicokinetic and pharmacokinetics using cases as illustration. Part 2 of this series focuses on key concepts related to distribution in the setting of overdose.

Case. 35-year-old female presents with severe iron overdose 4 hours post ingestion. Her VBG shows acidemia with pH of 7.2. Serum iron level is 95 µmol/L (chelation threshold for deferoxamine is >90 µmol/L).

Question: Why is deferoxamine most effective in the first 24 hours?

Answer: In addition to the increased risk of ARDS with deferoxamine use beyond 24 hours post iron ingestion, it is less likely to be helpful as there is less iron available in the blood compartment to chelate due to the distribution of iron into tissue as seen in the figure below.

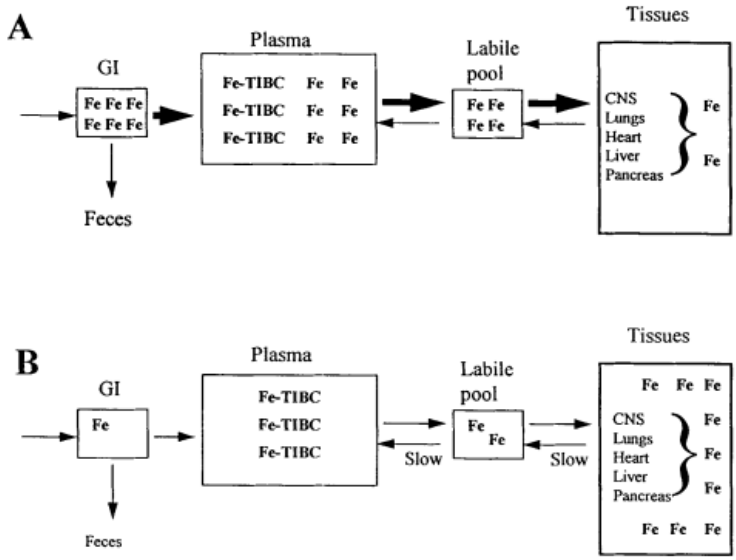

Figure 1. Conceptual diagram of the toxicokinetics of iron and the utility of deferoxamine. Panel A: In the first 24 h of iron poisoning there is free iron in the plasma with rapid distribution to the tissues. During this time frame iron in the plasma is easily accessible to deferoxamine. Panel B: After 24 h of iron poisoning, relatively little iron is directly accessible to deferoxamine from the plasma or indirectly from the tissues and the labile pool.

(Howland 1996)

Pearls:

- ✓ Once absorbed, many toxins undergo the process of distribution to compartments outside the blood (larger volume of distribution, Vd) which makes them less accessible to treatments aimed at eliminating the drug from the blood compartment (such as hemodialysis, chelation).
- ✓ The process of distribution results in a decline in serum concentration (in addition to metabolism and elimination). Be mindful that when evaluating the serum concentration of a drug, a decline in serum concentration does not always mean a decline in total body burden.

- ✓ Chronic poisonings of certain drugs (such as salicylate and lithium) often have a higher total body burden of toxins than acute poisonings for a similar serum concentration as more time has elapsed to allow distribution to occur. Therefore, treatment thresholds based on serum concentration is often lower for chronic compared to acute poisonings (for example, hemodialysis for chronic salicylate poisoning is often recommended if serum concentration is > ~ 4 mmol/L vs. acute salicylate poisoning > ~7 mmol/L).

Other key concepts related to distribution in toxicokinetics:

- ✓ Site of distribution ≠ site of action/toxicity.
  - Certain xenobiotics distribute to sites that are not active, such as lead to bone, or DDT to fat. Distribution in these cases is protective. Mobilization of toxins from these inactive sites of distribution can worsen toxicity. This was seen in a case of a single dose of $CaNa_2EDTA$ in lead poisoned rats which showed increased brain lead concentration. This suggests $CaNa_2EDTA$ may initially mobilize lead and facilitate redistribution to the brain (Cory-Slechta et al., 1987).
  - In comparison, certain xenobiotics distribute to sites that are active, such as CO to hemoglobin, or paraquat to type II alveolar cells of the lung. Distribution in these cases results in toxicity.
- ✓ Protein binding becomes saturated in overdose resulting in significant increase in free fraction of drugs.
  - Notable drugs with high protein binding include carbamazepine, valproate, warfarin, verapamil, phenytoin, and salicylate.
  - Drugs with high protein binding typically are not amenable to removal through dialysis. However, in overdose, the saturation of protein binding and the resultant increase in free fraction can make a drug more dialyzable. Valproate is a classic example of this where dialysis is used in overdose despite its high protein binding in therapeutic dose.
- ✓ Overdose can increase the apparent volume of distribution.
  - Saturation of protein binding in salicylate overdose causes an increase in the free fraction of drugs, which allows more diffusion through membranes (increased volume of distribution), more drug in tissues and an increase in toxicity.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

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.

Reference:

- ACMT Toxicology Board Review Course 2020.
- Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition
- Goldfrank's Toxicologic Emergencies, Eleventh Edition.
- Howland MA. Risks of parenteral deferoxamine for acute iron poisoning. J Toxicol Clin Toxicol. 1996;34(5):491-7. doi: 10.3109/15563659609028006. PMID: 8800186.
- Cory-Slechta DA, Weiss B, Cox C. Mobilization and redistribution of lead over the course of calcium disodium ethylenediamine tetraacetate chelation therapy. J Pharmacol Exp Ther. 1987 Dec;243(3):804-13. PMID: 3121845.