

Toxicokinetics

Introduction to Toxicokinetics

Definition of Toxicokinetics

- Toxicokinetics is the study of how a toxic substance (drug, chemical, poison) is absorbed, distributed, metabolized, and eliminated (ADME) by the body, particularly in overdose or poisoning scenarios.
- In simpler terms, it's the kinetic behavior of a toxin in the body, especially when normal pharmacokinetics no longer apply due to high doses, enzyme saturation, or organ dysfunction.

Importance of Toxicokinetics in Clinical Toxicology

- **Understanding toxicokinetics helps clinicians to:**
 - Predict onset, duration, and severity of toxic effects
 - Determine timing of decontamination and antidote therapy
 - Guide monitoring, drug level interpretation, and treatment decisions
 - Know when to initiate elimination enhancement techniques
 - Anticipate delayed toxicity or prolonged half-life

Phases of Toxicokinetics (ADME)

Toxicokinetics follows the same phases as pharmacokinetics but under toxic conditions.

A. Absorption

- The process by which a toxin enters the bloodstream from the site of exposure (oral, inhalation, dermal, etc.)
- **Alterations in overdose:**
 - Delayed gastric emptying (e.g., opioids, anticholinergics)
 - Prolonged absorption with sustained-release or enteric-coated formulations
 - Drug-induced pylorospasm (e.g., salicylates)
 - Formation of **pharmacobezoars** (drug concretions in the stomach)

B. Distribution

- The movement of a toxin from the bloodstream into tissues and organs
- Measured by Volume of Distribution (Vd)

Toxins with Low Vd (<1 L/kg)	Toxins with High Vd (>1 L/kg)
Lithium, Ethanol, Salicylate	Tricyclic antidepressants, Digoxin, Chloroquine

- High Vd drugs are not effectively removed by dialysis
- In overdose, plasma protein binding may become saturated, increasing free (active) drug levels

C. Metabolism

- Transformation of the toxin by liver enzymes, especially cytochrome P450 (CYP) system
- **May produce:**
 - **Inactive metabolites** (detoxification)
 - **Toxic metabolites** (bioactivation), e.g.:
 - Acetaminophen → NAPQI
 - Methanol → Formic acid
 - Ethylene glycol → Oxalic acid
- **Saturation of metabolic pathways** in overdose may:
 - Prolong half-life
 - Shift metabolism to toxic pathways

D. Elimination

- Removal of toxins via renal, hepatic, or pulmonary routes
- **Governed by:**
 - Clearance
 - Half-life
 - First-order vs zero-order kinetics

Key Toxicokinetic Parameters

Parameter	Definition	Clinical Relevance
Bioavailability (F)	Fraction of dose reaching systemic circulation	May be altered in poisoning (e.g., delayed absorption)
Volume of Distribution (Vd)	Ratio of drug in body vs blood	Low Vd → dialyzable; High Vd → not dialyzable
Clearance (Cl)	Volume of plasma cleared of toxin per time	Determines elimination rate
Half-life ($t_{1/2}$)	Time to eliminate 50% of toxin	Overdose may prolong half-life
Protein Binding	Portion bound to plasma proteins (e.g., albumin)	Only free drug is active; saturation increases toxicity
First-order kinetics	Constant fraction eliminated per unit time	Applies to most drugs at therapeutic levels

Zero-order kinetics	Constant amount eliminated per unit time (saturation kinetics)	Occurs in overdose; elimination slower and unpredictable
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Alterations in Toxicokinetics During Overdose

- In overdose, toxicokinetics frequently deviate from therapeutic pharmacokinetics due to saturation of physiological processes.

Process	Therapeutic Doses	Overdose
Absorption	Rapid, complete	Delayed, prolonged
Protein binding	Linear	Saturation increases free drug
Metabolism	First-order	May become zero-order
Elimination	Predictable	Slowed, prolonged half-life

Examples:

- **Phenytoin:** Therapeutic = first-order; Toxic = zero-order
- **Ethanol, Salicylates, Theophylline:** Exhibit zero-order kinetics in overdose
- **Paracetamol (Acetaminophen):** Saturation of glucuronidation → shunted to CYP → toxic metabolite (NAPQI)

Clinical Applications of Toxicokinetics

1. Predicting Toxicity

- Knowledge of toxic dose and Vd helps estimate risk
- E.g., lithium overdose: low Vd → good candidate for dialysis

2. Antidote Timing and Dosing

- NAC in paracetamol poisoning: effective if given before toxic metabolite accumulates
- Fomepizole: blocks toxic metabolism of methanol/ethylene glycol

3. Determining Duration of Monitoring

- Long half-life in overdose → longer observation period
- Sustained-release drug ingestions → extended monitoring

4. Choosing Elimination Enhancement Techniques

- Based on Vd, protein binding, and molecular weight:
 - Low Vd + low protein binding → Dialysis
 - High Vd + enterohepatic recirculation → MDAC

5. Interpreting Drug Levels

- Important in substances with **delayed absorption** (e.g., salicylates)

- Serial levels often required to assess peak toxicity



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