# 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 (t½)** | 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 |

## 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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