TOXICOLOGY II

Lecture – 9

Second Semester

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Course Description

This course introduces the fundamental principles of pharmacology, focusing on:

- Drug classification systems
- Mechanisms of drug action
- Pharmacokinetics (ADME)
- Pharmacodynamics
- Drug–drug interactions
- Toxicology and drug safety

Week	Topic
1	Introduction to Pharmacology
2	Pharmacokinetics (ADME)
3	Pharmacodynamics
4	Steroid & Non-Steroid Drugs
5	Nervous System Pharmacology
6	Cardiovascular Pharmacology
7	Antimicrobial Agents
8	Endocrine & Metabolic Drugs
9	Hematology & Chemotherapy
10	General Toxicology
11	Clinical Toxicology & Drug Safety
12	Student Presentations & Review

COURSE SYLLABUS

Learning Objectives

- Toxicity
- Toxicokinetics
- Toxicodynamics

Toxicology

Toxicology studies the harmful effects of chemicals, drugs, toxins, and environmental agents on living organisms.

- Why substances become toxic
- How poisons damage tissues
- Safe versus dangerous drug doses
- Prevention and treatment of poisoning

- Pharmacology studies therapeutic effects of drugs, while toxicology studies adverse and harmful effects.

- Principle: Every substance can become toxic if the dose is high enough.

Toxicokinetics (TK)

- Toxicokinetics is the branch of toxicology that studies the time-dependent movement of toxic substances within the body.
- It describes how a chemical or toxin is absorbed, distributed, metabolized, and excreted (**ADME**) after exposure.

Toxicokinetics helps determine:

- The concentration of toxins in tissues and blood
- Duration of exposure
- Bioavailability of toxic compounds
- Rate of elimination
- Accumulation within organs

Main Components of Toxicokinetics (ADME)

A. Absorption

Absorption is the process by which a toxic substance enters systemic circulation from the site of exposure.

Route	Description	Example
Oral	Through gastrointestinal tract	Food contaminants
Inhalation	Through lungs	Carbon monoxide
Dermal	Through skin	Pesticides
Injection	Direct entry into blood/tissues	Snake venom

Mechanisms of Absorption

Toxins cross biological membranes through:

- Passive diffusion
- Facilitated diffusion
- Active transport
- Endocytosis

Factors Affecting Absorption

- Surface area
- Blood flow
- Exposure duration
- Chemical formulation
- Presence of food
- Skin integrity

Main Components of Toxicokinetics (ADME)

B. Distribution

Distribution refers to the reversible transfer of toxins from the bloodstream into tissues and organs.

After absorption, toxins circulate through blood and distribute according to:

- Blood supply
- Tissue affinity
- Lipid solubility
- Protein binding

Volume of Distribution (Vd):

The volume of distribution estimates how extensively a toxin disperses throughout the body.

$$V_d = \frac{Amount\ of\ toxin\ in\ body}{Plasma\ concentration}$$

Large Vd indicates:

- Extensive tissue distribution
- Lipophilic compounds
- Tissue accumulation

Main Components of Toxicokinetics (ADME)

B. Distribution

Organ Accumulation

Toxin	Major Organ
Lead	Bone
Mercury	Kidney
Organophosphates	Nervous system
Carbon tetrachloride	Liver

Main Components of Toxicokinetics (ADME)

C. Metabolism (Biotransformation)

- Metabolism is the enzymatic conversion of toxic compounds into more water-soluble metabolites to facilitate elimination.
- The liver is the major organ responsible for metabolism.

Objectives of Metabolism

- Detoxification
- Increase excretion
- Reduce lipid solubility

However, metabolism can sometimes produce more toxic metabolites.

Main Components of Toxicokinetics (ADME)

D. Excretion

- Excretion is the removal of toxins and metabolites from the body.
- Major Routes:

Route	Example
Kidney (urine)	Heavy metals
Liver/bile	Steroid toxins
Lungs	Volatile compounds
Sweat	Trace chemicals
Breast milk	Lipid-soluble toxins

Renal Excretion

Kidneys eliminate toxins through:

1. Glomerular filtration
2. Tubular secretion
3. Tubular reabsorption

Urinary pH significantly affects excretion.

Ion Trapping:
Weak acids become ionized in alkaline urine and are excreted more efficiently.

Main Components of Toxicokinetics (ADME)

D. Excretion

Elimination Half-Life

Half-life is the time required for the toxin concentration to decrease by 50%.

$$t_{1/2} = \frac{0.693 \times V_d}{Cl}$$

Where:

- V_d =volume of distribution
- Cl= clearance

Longer half-life leads to:

- Greater accumulation
- Prolonged toxicity

Toxicodynamics (TD)

Toxicodynamics studies the molecular, biochemical, and physiological effects of toxic substances on biological systems.

It explains:

- Mechanisms of toxicity
- Cellular injury
- Organ dysfunction
- Dose–response relationships

Toxicodynamics focuses on the interaction between toxins and:

- Receptors
- Enzymes
- DNA
- Cell membranes
- Organelles

Toxicodynamics (TD)

Mechanisms of Toxicity

A. Receptor-Mediated Toxicity

- Some toxins bind specific cellular receptors and alter signaling pathways.

Example

- Dioxins bind aryl hydrocarbon receptors (AhR), altering gene expression and immune responses.

B. Enzyme Inhibition

Toxins may inhibit essential enzymes.

Example
Organophosphates inhibit acetylcholinesterase.

Result:

- Acetylcholine accumulation
- Continuous nerve stimulation
- Paralysis

Toxicodynamics (TD)

DNA Damage and Mutagenesis

Certain toxins directly damage genetic material. Consequences:

- Mutations
- Chromosomal abnormalities
- Cancer development

Example

- Benzene metabolites induce bone marrow DNA damage.

Toxicodynamics (TD)

Mitochondrial Dysfunction

Toxins can impair ATP production.

Result:

- Cellular hypoxia
- Energy failure
- Cell death

Example

- Cyanide inhibits cytochrome oxidase in mitochondria.

Toxicodynamics (TD)

Dose–Response Relationship

The relationship between toxin dose and biological effect.

$$E = \frac{E_{max} \times C}{EC_{50} + C}$$

Where:

- E= effect
- E_{max} =maximum effect
- C= concentration
- EC_{50} =concentration producing 50% effect

Types of Toxic Responses

Type	Description
Graded response	Effect increases with dose
Quantal response	All-or-none response

Examples:

Graded: Liver enzyme elevation
Quantal: Death or seizure occurrence

Toxicodynamics (TD)

Target Organ Toxicity

Different organs exhibit varying sensitivity.

Organ	Common Toxicants
Liver	Acetaminophen
Kidney	Mercury
Brain	Lead
Lung	Asbestos
Bone marrow	Benzene

Therapeutic Index

Measures drug safety margin.

$$TI = \frac{LD_{50}}{ED_{50}}$$

Higher TI:

- Safer compound

Lower TI:

- Greater toxicity risk

Relationship Between Toxicokinetics and Toxicodynamics

Toxicokinetics	Toxicodynamics
What the body does to toxin	What toxin does to body
ADME processes	Mechanisms of injury
Determines tissue concentration	Determines biological effect
Influences exposure duration	Influences toxicity severity

Summary

Toxicokinetics determines:

- How toxins move through the body
- How long they remain
- Their concentration within organs

Toxicodynamics determines:

- How toxins damage cells
- Mechanisms of toxicity
- Physiological consequences

References

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- *Essentials of Toxicology. Academic Press; 2016.*
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