TOXICOLOGY

Lecture – 8

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
- Understanding of Carcinogen, Teratogen, and Mutagen
- Dose–Response Relationship
- Routes of Toxic Exposure

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.

Relationship Between Pharmacology and Toxicology

Pharmacology	Toxicology
Beneficial drug effects	Harmful effects
Therapeutic dose	Toxic dose
Drug mechanism	Toxic mechanism
Disease treatment	Poison management

- A drug that is therapeutic at one dose may become toxic at a higher dose.
- Paracetamol relieves pain at normal doses but causes liver failure in overdose.

Major Branches of Toxicology

Branch	Main Focus
Clinical Toxicology	Human poisoning
Environmental Toxicology	Pollution and environmental hazards
Forensic Toxicology	Legal investigations
Occupational Toxicology	Workplace exposures
Pharmaceutical Toxicology	Drug safety testing

Clinical Toxicology

Clinical Toxicology is the branch of toxicology and medicine that focuses on the diagnosis, treatment, and prevention of poisoning and toxic effects caused by drugs, chemicals, toxins, environmental substances, and biological agents in humans.

Common Areas in Clinical Toxicology

Area	Examples
Drug poisoning	Paracetamol overdose, opioids
Chemical exposure	Pesticides, cyanide
Environmental toxins	Lead, mercury
Substance abuse	Alcohol, cocaine
Snake/insect envenomation	Snake bites, scorpion stings
Occupational toxicity	Industrial chemicals

Basic Toxicology Terminology

Term	Definition
Toxin	Natural poison produced by organisms
Toxicant	Harmful synthetic chemical
Poison	Substance causing injury/death
Antidote	Substance that counteracts poison
LD50	Lethal dose killing 50% of animals

Understanding of Carcinogen, Teratogen, and Mutagen

Many chemicals, drugs, radiation sources, and environmental agents can damage human health at the genetic or cellular level. In toxicology and pharmacology, three important terms are commonly discussed:

- **Carcinogens,**
- **Teratogens, and**
- **Mutagens.**

Carcinogen

- A carcinogen is any substance, chemical, radiation, or biological agent that can cause cancer by promoting uncontrolled cell growth.
- An agent capable of inducing cancer in living tissues

Understanding of Carcinogen, Teratogen, and Mutagen

Mechanism of Carcinogenesis

Carcinogens may:

- Damage DNA
- Cause gene mutations
- Activate oncogenes
- Inactivate tumor suppressor genes
- Promote chronic inflammation
- Increase abnormal cell proliferation

Types of Carcinogens

Type	Examples
Chemical carcinogens	Tobacco smoke, asbestos, benzene
Physical carcinogens	UV radiation, X-rays
Biological carcinogens	HPV, HBV, H. pylori

Examples

- Cigarette smoke ⟶ lung cancer
- UV radiation ⟶ skin cancer
- Asbestos ⟶ mesothelioma
- Human papillomavirus (HPV) ⟶ cervical cancer

Understanding of Carcinogen, Teratogen, and Mutagen

Characteristics

- Usually long-term exposure required
- Cancer development may take years
- Dose and duration influence risk

Important Concept

Not all carcinogens directly mutate DNA. Some act as:

- **Initiators** → cause mutation
- **Promoters** → stimulate cancer growth

Teratogen

A **teratogen** is an agent that causes abnormal fetal development during pregnancy.

Mechanism

Teratogens interfere with:

- Cell division
- Organ formation
- Tissue differentiation
- Embryonic development

Effects of Teratogens

- Congenital malformations
- Growth retardation
- Mental impairment
- Functional abnormalities
- Miscarriage

Examples of Teratogens

Teratogen	Fetal Effect
Alcohol	Fetal alcohol syndrome
Thalidomide	Limb defects
Isotretinoin	Craniofacial abnormalities
Radiation	CNS defects
Rubella virus	Congenital heart defects

Mutagen

A **mutagen** is an agent that causes permanent changes (mutations) in DNA.

Mechanism

Mutagens can:

- Break DNA strands
- Alter nucleotide sequences
- Cause insertions or deletions
- Produce chromosomal abnormalities

Types of Mutagens

Type	Examples
Chemical mutagens	Nitrosamines, alkylating agents
Physical mutagens	UV light, ionizing radiation
Biological mutagens	Certain viruses

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Mutagen

Consequences of Mutations

- Cancer
- Genetic diseases
- Cell death
- Drug resistance

Examples

- UV radiation → thymine dimers
- X-rays → DNA strand breaks
- Benzene metabolites → chromosomal damage

Relationship Between Carcinogens, Teratogens, and Mutagens

Property	Carcinogen	Teratogen	Mutagen
Main Effect	Cancer	Fetal abnormalities	DNA mutations
Target	Somatic cells	Embryo/fetus	Genetic material
May alter DNA?	Often	Sometimes	Yes
Heritable effect	Usually no	Developmental	Possible

Important Facts

- Many mutagens are also carcinogens
- Some carcinogens act through mutagenesis
- Some teratogens also cause mutations
- Not all mutagens cause cancer
- Not all carcinogens are mutagens

Dose–Response Relationship

- The dose–response relationship describes the relationship between the amount of a substance (dose) and the magnitude of the biological or toxic effect (response) it produces in the body.

Principle

"As the dose increases, the intensity or frequency of the effect usually increases."

- Small doses may produce little or no effect
- Moderate doses produce therapeutic or toxic effects
- High doses can cause severe toxicity or death

Importance of Dose–Response Relationship

It helps determine:

- Safe drug dosage
- Toxic dose
- Lethal dose
- Therapeutic window
- Drug potency and efficacy
- Safety limits for chemicals

Basic Dose–Response Curve

Typically:

- X-axis = Dose
- Y-axis = Response

As dose increases:

1. No effect region
2. Threshold reached
3. Increasing response
4. Maximum response plateau

Types of Responses

1. Graded Response:

A **graded response** is a response that increases gradually as the dose increases.

Characteristics

- Measured in a single individual
- Response varies continuously
- Magnitude of effect changes progressively

Dose	Effect
Low dose antihypertensive drug	Slight blood pressure reduction
Higher dose	Greater blood pressure reduction

Other examples:

- Heart rate reduction
- Pain relief
- Muscle relaxation
- Enzyme inhibition

Key Point

The response is proportional to the dose up to a maximum effect.

Types of Responses

2. Quantal Response

A quantal response is an all-or-none effect.

The effect either:

- Occurs, or
- Does not occur

Characteristics

- Measured in a population
- Used to determine toxicity and lethality
- Expressed as percentage of individuals responding

Important Toxicological Terms

- **ED50 (Effective Dose 50)**
  Dose producing therapeutic effect in 50% of the population.
- **TD50 (Toxic Dose 50)**
  Dose causing toxicity in 50% of the population.
- **LD50 (Lethal Dose 50)**
  Dose causing death in 50% of experimental animals.

Therapeutic Index (TI)

Measures drug safety.

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

Interpretation

- High TI ⟶ safer drug
- Low TI ⟶ higher risk of toxicity

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Factors Affecting Dose–Response Relationship

Factor	Influence
Age	Children and elderly more sensitive
Body weight	Alters drug concentration
Genetics	Different metabolism
Route of exposure	Oral vs IV vs inhalation
Duration of exposure	Acute vs chronic toxicity
Drug interactions	May increase toxicity

Routes of Toxic Exposure

Main Routes

Route	Example
Oral	Drug overdose
Inhalation	Toxic gases
Dermal	Pesticides
Injection	Venoms
Ocular	Chemical splashes

Important Factors

Toxicity depends on:

- Dose
- Duration
- Route of exposure
- Patient age
- Liver/kidney function

Process	Definition	Main Organs Involved	Important Factors	Example
Absorption	Movement of toxin from exposure site into blood	Skin, lungs, stomach, intestine	Lipid solubility, pH, dose, route	Carbon monoxide inhalation
Distribution	Transport of toxin to tissues and organs	Blood, liver, brain, fat tissue	Blood flow, protein binding	Lead accumulation in bone
Metabolism	Chemical conversion of toxin into metabolites	Liver (mainly)	Liver enzymes, age, genetics	Acetaminophen → NAPQI
Excretion	Elimination of toxin from body	Kidney, liver, lungs	Kidney function, urine pH	Methanol excreted in urine

Toxicokinetics

- **Toxicokinetics** is the study of how a toxic substance enters, moves through, changes within, and leaves the body over time.

Summary

- Toxicology studies harmful effects of drugs and chemicals.
- It explains poisoning, overdose, and toxicity mechanisms.
- “The dose makes the poison.” — Paracelsus
- Toxicokinetics = ADME (absorption, distribution, metabolism, excretion).

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