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BIOPHARMACEUTICS AND PHARMACOKINETICS

UNIT 3

TOPIC :

- **Pharmacokinetics :** Definition and introduction to Pharmacokinetics, Compartment models, Non compartment models, physiological models, One compartment open model. (a). Intravenous Injection (Bolus) (b). Intravenous infusion and (c) Extra vascular administrations. Pharmacokinetics parameters- KE ,t1/2,Vd,AUC,Ka, Clt and
  CLR- definitions methods of eliminations, understanding of their significance and application

Pharmacokinetics

Pharmacokinetics is the branch of science that studies what the body does to a drug after administration.

It explains how a drug moves through the body from the time it is administered until it is eliminated from the body.

Pharmacokinetics helps in understanding:

- Drug absorption
- Drug distribution
- Drug metabolism
- Drug excretion

Pharmacokinetics is commonly known as ADME.

ADME PROCESS

1. Absorption

Absorption is the process by which a drug moves from its site of administration into systemic circulation.

It determines:

- Rate of drug entry into blood
- Extent of drug reaching circulation

Factors Affecting Absorption

- Route of administration
- Solubility
- Blood flow
- GI motility
- pH

2. Distribution

Distribution is the process by which the drug spreads from blood to tissues and organs.

After absorption, the drug is transported throughout the body through circulation.

Factors Affecting Distribution

- Blood flow to tissues
- Protein binding
- Lipid solubility
- Tissue permeability

3. Metabolism

Metabolism is the biochemical conversion of drugs into simpler and more water-soluble forms.

It mainly occurs in the liver.

Purpose

- Detoxification
- Facilitate excretion

Types

- Phase I reactions
- Phase II reactions

4. Excretion

Excretion is the removal of drugs and metabolites from the body.

Major route:

- Kidneys through urine

Other routes:

- Bile
- Sweat
- Saliva
- Lungs
- Breast milk

Objectives of Pharmacokinetics

1. To study absorption of drugs
2. To determine drug distribution in body
3. To understand metabolism of drugs
4. To study elimination and excretion
5. To calculate plasma drug concentration over time
6. To optimize drug dosage regimen
7. To achieve maximum therapeutic effect with minimum toxicity
8. To support therapeutic drug monitoring
9. To predict onset, intensity and duration of drug action

Applications Of Pharmacokinetics

1. Dose Determination

Helps decide:

- Dose size
- Frequency of administration

2. Therapeutic Drug Monitoring

Maintains drug concentration within therapeutic range.

3. Prevention of Toxicity

Helps avoid:

- Drug accumulation
- Side effects
- Toxic reactions

4. Individualization of Therapy

Drug therapy can be adjusted according to:

- Age
- Weight
- Organ function
- Disease condition

5. Drug Development

Useful in:

- Formulation design

- Bioavailability studies

Pharmacokinetic Models

Pharmacokinetic models are mathematical models used to describe and predict the movement of drugs in the body over time.

These models explain:

- How a drug enters the body
- How it distributes
- How it is metabolized
- How it is eliminated

Pharmacokinetic models simplify the body into compartments or systems to study drug behavior.

Definition

A pharmacokinetic model is a hypothetical representation of the body used to analyze drug concentration changes with time.

These models help scientists understand ADME processes:

- Absorption
- Distribution
- Metabolism
- Excretion

Objectives of Pharmacokinetic Models

1. To predict drug concentration in the body
2. To understand drug movement and elimination
3. To calculate pharmacokinetic parameters
4. To design proper dosage regimens

5. To optimize therapeutic response
6. To minimize toxicity

Methods for Analysis of Pharmacokinetic Data

There are two main approaches:

1. Model Dependent Approach

(Compartmental Analysis)

2. Model Independent Approach

(Non-Compartmental Analysis)

1. Model Dependent Approach

This method assumes that the body behaves as one or more compartments.

Types include:

- Compartment Models
- Physiological Models

Compartment Models

Compartment models divide the body into imaginary compartments where the drug distributes uniformly.

A compartment is not an actual organ but a hypothetical group of tissues having similar:

- Blood flow
- Drug affinity

Characteristics of Compartment Models

- Simple and easy to understand
- Drug concentration assumed uniform in each compartment
- Drug movement represented using mathematical equations

Advantages of Compartment Models

- Simple to use
- Predict drug concentration over time
- Useful for estimating absorption and elimination
- Require less experimental data
- Help design dosage schedules

Disadvantages of Compartment Models

- Do not represent real organs
- Less accurate for complex drug distribution
- Not suitable for all drugs
- Oversimplifies body functions

Types of Compartment Models

1. Mammillary Model
2. Catenary Model

1. Mammillary Model

Mammillary model is the most commonly used pharmacokinetic model.

It contains:

- One central compartment
- One or more peripheral compartments

Peripheral compartments are connected directly to the central compartment.

Central Compartment

Includes:

- Blood plasma
- Highly perfused organs

Examples:

- Liver
- Kidneys
- Lungs

Peripheral Compartment

Includes:

- Less vascular tissues
- Fat
- Muscle

Drug distribution is slower here.

Rate Constants

Movement of drug between compartments is represented by rate constants.

Examples:

- K12 → Central to peripheral compartment
- K21 → Peripheral to central compartment
- K10 → Elimination from central compartment

Types of Mammillary Models

A. One-Compartment Open Model

In this model:

- Entire body acts as one compartment
- Drug distributes rapidly and uniformly

Drug elimination occurs from the compartment.

One-Compartment Open Model with IV Injection

Drug directly enters systemic circulation.

C = C_o e^{-kt}

Where:

- C = Drug concentration at time t
- C_0 = Initial concentration
- k = Elimination rate constant

Features

- Simplest pharmacokinetic model
- Used for rapidly distributing drugs

B. One-Compartment Open Model with First Order Absorption

Used for:

- Oral administration

Drug first undergoes absorption and then elimination.

C. Two-Compartment Open Model

In this model:

- Body divided into:
  - Central compartment
  - Peripheral compartment

Drug first enters central compartment and later distributes into peripheral compartment.

Two-Compartment Open Model for IV Injection

Drug distribution and elimination occur simultaneously.

Characteristics

- More realistic than one-compartment model
- Plasma concentration declines in two phases:
  - Distribution phase
  - Elimination phase

Two-Compartment Open Model with First Order Absorption

Used for orally administered drugs showing:

- Distribution
- Absorption
- Elimination

2. Catenary Model

Catenary model is a chain-like compartment model where compartments are connected one after another.

Drug passes sequentially through compartments.

Characteristics

- Less commonly used
- Represents sequential drug movement

Advantages

- Useful for certain specialized studies

Disadvantages

- Complex calculations
- Rarely used in practice

Physiological Models

Physiological models are also called:

- Physiologically Based Pharmacokinetic Models (PBPK Models)

These models describe drug distribution in the body in a more realistic manner using:

- Anatomical data
- Physiological data
- Blood flow information

Unlike compartment models, physiological models attempt to represent actual organs and tissues.

Definition

Physiological models are pharmacokinetic models based on real physiological and anatomical characteristics of the body to predict drug concentration in tissues and organs.

These models help predict:

- Tissue drug concentration
- Drug distribution
- Drug elimination

more accurately than simple compartment models.

Characteristics of Physiological Models

- Based on real organs and tissues
- Use actual blood flow data
- Include tissue size and composition
- Use mathematical equations for each organ

Structure of Physiological Models

In these models:

- Each organ or tissue is represented by a compartment.
- Compartments are connected through blood circulation.

Because describing every organ separately becomes complex, tissues with similar blood perfusion are grouped together.

Factors Affecting Drug Distribution in Physiological Models

1. Blood Flow to Organs

Higher blood flow increases drug delivery to tissues.

2. Tissue Permeability

Drug entry depends on:

- Lipid solubility
- Membrane transport
- Degree of ionization

3. Tissue Composition

Drug distribution depends on:

- Fat content
- Water content
- Protein binding

Types of Physiological Models

There are mainly two types:

1. Perfusion Limited Model
2. Diffusion Limited Model

1. Perfusion Limited Model

(Blood Flow Rate Limited Model)

In this model, drug distribution depends mainly on blood flow to tissues.

The drug crosses cell membranes rapidly, so blood flow becomes the rate-limiting step.

Characteristics

- Suitable for lipid soluble drugs
- Drug movement across membrane is rapid
- Distribution controlled by tissue perfusion

Applications

Useful for:

- Non-ionized drugs
- Highly permeable drugs

2. Diffusion Limited Model

(Membrane Permeation Rate Limited Model)

In this model, drug distribution depends mainly on membrane permeability and diffusion.

Cell membrane acts as barrier for drug movement.

Characteristics

- Drug crosses membrane slowly
- Membrane permeability is rate-limiting step

Suitable For

- Polar drugs
- Ionized drugs
- Charged molecules

2. Model Independent Approach

(NON-COMPARTMENTAL ANALYSIS)

Non-compartmental analysis is a pharmacokinetic method that does not assume any specific compartment model.

It is also called:

- Model independent approach

Characteristics

- Based on statistical moment theory
- Uses experimental plasma concentration data
- Assumes linear pharmacokinetics

Principle

After administration of a single dose:

- Plasma drug concentration is measured over time
- Pharmacokinetic parameters are calculated directly from concentration-time curve

Determination of AUC and AUMC

AUC and AUMC are calculated using:

- Trapezoidal rule

In this method:

- Curve divided into trapezoids
- Area of each trapezoid calculated separately
- Total areas added together

Advantages of Non-Compartmental Analysis

- Simple mathematical calculations
- No need to assume compartments
- Useful for many drugs following first-order kinetics
- Requires fewer assumptions

One Compartment Open Model

The one compartment open model is the simplest pharmacokinetic model used to describe drug distribution and elimination.

In this model:

- The body acts as a single uniform compartment.
- Drug distributes instantly and uniformly throughout the body.
- Drug elimination occurs from the compartment.

It is called:

- **One compartment** → because the body behaves as one unit.
- **Open model** → because drug can leave the body through elimination.

Assumptions of One Compartment Open Model

1. Drug distributes rapidly throughout the body
2. Drug concentration is uniform in all tissues
3. Elimination follows first-order kinetics
4. Drug elimination occurs from central compartment

Types of One Compartment Open Model

1. Intravenous Bolus Injection
2. Intravenous Infusion
3. Extravascular Administration

(A) One Compartment Open Model – Intravenous Bolus Injection

In IV bolus injection:

- Entire dose is administered directly into bloodstream instantly.

Absorption phase is absent.

Bioavailability is 100%.

Plasma Concentration-Time Profile

Drug concentration decreases exponentially due to elimination.

$$C = C_0 e^{-K_E t}$$

Where:

- C = Drug concentration at time t
- C_0 = Initial concentration
- KE = Elimination rate constant
- t = Time

Characteristics

- Rapid onset of action
- No absorption phase
- Suitable for emergency conditions

Advantages

- Complete bioavailability
- Accurate dose control

Disadvantages

- Risk of toxicity
- Requires trained personnel

(B) One Compartment Open Model – Intravenous Infusion

In IV infusion:

- Drug is administered slowly and continuously into bloodstream at constant rate.

Characteristics

- Plasma concentration gradually increases
- Steady state concentration achieved after some time

Steady State Concentration

Occurs when:

- Rate of drug administration = Rate of drug elimination

Equation for IV Infusion

$$C = \frac{K_0}{V_d K_E}\left(1 - e^{-K_E t}\right)$$

Where:

- K_0 = Infusion rate
- Vd = Volume of distribution
- KE = Elimination rate constant

Advantages

- Maintains constant plasma concentration
- Useful for drugs with short half-life

Disadvantages

- Requires monitoring
- Risk of infusion reactions

(C) One Compartment Open Model – Extravascular Administration

Extravascular administration includes:

- Oral
- Intramuscular
- Subcutaneous routes

Drug must first undergo absorption before reaching systemic circulation.

Characteristics

- Includes absorption phase
- Bioavailability may be incomplete

Plasma Concentration Equation

$$C = \frac{FDK_a}{V_d(K_a - K_E)} \left(e^{-K_E t} - e^{-K_a t}\right)$$

Where:

- F = Bioavailability
- D = Dose
- Ka = Absorption rate constant
- KE = Elimination rate constant
- Vd = Volume of distribution

Phases

1. Absorption phase
2. Peak concentration phase
3. Elimination phase

Pharmacokinetic Parameters

1. Elimination Rate Constant (Ke)

KE is the fraction of drug eliminated from the body per unit time.

Formula

$$K_E = \frac{0.693}{t_{1/2}}$$

Significance

- Indicates speed of drug elimination
- Helps determine dosing interval

2. Biological Half-Life (T½)

Half-life is the time required for plasma drug concentration to reduce to half its original value.

Formula

$$t_{1/2} = \frac{0.693}{K_E}$$

Significance

- Determines duration of action
- Helps calculate dosing frequency

3. Volume of Distribution (Vd)

Volume of distribution is the apparent volume in which drug distributes in the body.

Formula

$$V_d = \frac{Dose}{C_0}$$

Significance

- Helps determine loading dose
- Indicates extent of tissue distribution

4. Area Under Curve (AUC)

AUC represents total drug exposure over time.

Formula

$$AUC = \int_0^\infty C\,dt$$

Significance

- Measures extent of absorption
- Used in bioavailability studies

5. Absorption Rate Constant (Ka)

Ka is the rate constant for drug absorption into systemic circulation.

Significance

- Indicates speed of absorption
- Higher Ka means faster absorption

6. Total Body Clearance (Clt)

Clearance is the volume of plasma completely cleared of drug per unit time.

Formula

$$Cl_t = V_d \times K_E$$

Significance

- Indicates efficiency of elimination
- Helps determine maintenance dose

7. Renal Clearance (Clr)

Renal clearance is the volume of plasma cleared of drug by kidneys per unit time.

Formula

$$Cl_R = \frac{Rate\ of\ urinary\ excretion}{Plasma\ drug\ concentration}$$

Significance

- Indicates renal elimination efficiency
- Important in kidney disease

Methods of Elimination

Drug elimination mainly occurs through:

1. Renal Excretion

Through urine by kidneys.

2. Hepatic Metabolism

Drug converted into metabolites in liver.

3. Biliary Excretion

Drug excreted through bile into feces.

4. Pulmonary Excretion

Excretion through lungs.

Examples:

- Volatile anesthetics