UNIT 2

PHARMACOKINETICS-BASIC CONSIDERATIONS

Plasma Drug Concentration-Time Profile Plotting Data

S. SANGEETHA., M.PHARM., (Ph.d)
Department of Pharmaceutics
SRM College of Pharmacy
SRM University
INTRODUCTION TO PHARMACOKINETICS

• The duration of a drug therapy ranges from a single dose of a drug taken for relieving an acute condition such as headache to drugs taken life–long for chronic conditions such as hypertension, diabetes, asthma or epilepsy.

• The frequency of administration of a drug in a particular dose is called as **Dosage regimen**.

• Depending upon the therapeutic objective to be attained, the duration of drug therapy and the dosage regimen are decided.
Rational and optimal therapy with a drug depend upon:
1. Choice of a suitable drug, and
2. Balance between the therapeutic and the toxic-effects.

Both, the therapeutic and the toxic effects, depend upon the concentration of drug at the site of action which is difficult to measure. However, it corresponds to a specific concentration of drug in plasma which can be measured with accuracy.

The drug fails to elicit a therapeutic response when the concentration is below the effective level and precipitates adverse reactions when above the toxic level. The plasma drug concentration between these two limits is called as the **Therapeutic concentration range** or **Therapeutic window**.
• The ratio of maximum safe concentration to minimum effective concentration of the drug is called as the Therapeutic index.

• Thus, in order to achieve therapeutic success, plasma concentration of the drug should be maintained within the therapeutic window. For this, knowledge is needed not only of the mechanisms of drug absorption, distribution, metabolism and excretion, but also of the kinetics of these processes i.e. Pharmacokinetics.
Definitions

- **Pharmacokinetics** is defined as the kinetics of drug absorption, distribution, metabolism and excretion (KADME) and their relationship with the pharmacological, therapeutic or toxicological response in humans.

- **Absorption** is defined as the process of movement of unchanged drug from the site of administration to systemic circulation (or to the site of measurement i.e. plasma).

- **Distribution** is reversible transfer of a drug between the blood and the extra vascular fluids and tissues.
• **Elimination** is the major process for removal of a drug from the body and termination of its action. It is defined as the irreversible loss of drug from the body. Elimination occurs by two processes *viz.* biotransformation and excretion.

• **Metabolism (Biotransformation)** of drugs is defined as the chemical conversion of one form to another.

• **Excretion** is defined as the process whereby drugs and/or their metabolites are irreversibly transferred from internal to external environment.
Pharmacokinetic Studies

• There are two aspects of pharmacokinetic studies-

1. *Theoretical aspect*: which involves development of pharmacokinetic models to predict drug disposition after its administration. Statistical methods are commonly applied to interpret data and assess various parameters.

2. *Experimental aspect*: which involves development of biological sampling techniques, analytical methods for measurement of drug (and metabolites) concentration in biological samples and data collection and evaluation.
Several relevant terms:

*Clinical Pharmacokinetics* is defined as the application of pharmacokinetic principles in the safe and effective management of individual patient.

*Population Pharmacokinetics* is defined as the study of pharmacokinetic differences of drugs in various population groups.

*Toxicokinetics* is defined as the application of pharmacokinetic principles to the design, conduct and interpretation of drug safety evaluation studies.
A direct relationship exists between the concentration of drug at the biophase (site of action) and the concentration of drug in plasma. Two categories of parameters can be evaluated from a plasma concentration time profile:

- Pharmacokinetic parameters, and
- Pharmacodynamic parameters.

A typical plasma drug concentration-time curve obtained after a single oral dose of a drug and showing various pharmacokinetic and pharmacodynamic parameters is depicted in figure. Such a profile can be obtained by measuring concentration of drug in plasma samples taken at various intervals of time after administration of a dosage form and plotting the concentration of drug in plasma (Y-axis) versus the corresponding time at which the plasma sample was collected (X-axis).
Peak plasma conc.  
Cmax (absorption rate=elimination rate)

Onset of action
Intensity of action
Duration of action
Post-absorption phase

Area under the curve (AUC)

Onset time
Duration of action

Time for peak plasma conc.

Termination of action

Toxic level

Maximum Safe Conc. (MSC)

Therapeutic range

Minimum effective conc. (MEC)

Subtherapeutic level

Elimination Phase

Time

Plasma Drug Concentration-time Profile
Pharmacokinetic Parameters

• The three important pharmacokinetic parameters that describe the plasma level-time curve and useful in assessing the bioavailability of a drug from its formulation are-

1. **Peak Plasma concentration (Cmax):**

   The point of maximum concentration of drug in plasma is called as the **peak** and the concentration of drug at peak is known as **peak plasma concentration**. It is also called as **peak height concentration** and **maximum drug concentration**.

   Cmax is expressed in mcg/ml.
The peak level depends upon:
- Dose administered
- Rate of absorption, and
- Rate of elimination.

The peak represents the point of time when absorption rate equals elimination rate of drug. The portion of curve to the left of peak represents absorption phase *i.e. when the rate of absorption is greater than the rate of elimination*. The section of curve to the right of peak generally represents elimination phase *i.e. when the rate of elimination exceeds rate of absorption*. Peak concentration is often related to the intensity of pharmacological response and should ideally be above minimum effective concentration (MEC) but less than the maximum safe concentration (MSC).
2. Time of Peak Concentration (tmax):

The time for drug to reach peak concentration in plasma (after extravascular administration) is called as the **time of peak concentration**.

It is expressed in hours and is useful in estimating the rate of absorption.

Onset time and onset of action are dependent upon tmax.

The parameter is of particular importance in assessing the efficacy of drug used to treat acute conditions like pain and insomnia which can be treated by a single dose.
3. Area Under the Curve (AUC):

It represents the total integrated area under the plasma level-time profile and expresses the total amount of drug that comes into the systemic circulation after its administration.

AUC is expressed in mcg/ml * hours.

It is the most important parameter in evaluating the bioavailability of a drug from its dosage form as it represents the extent of absorption.

AUC is also important for drugs that are administered repetitively for the treatment of chronic conditions like asthma or epilepsy.
Pharmacodynamic Parameters

• The various Pharmacodynamic parameters are-

1. **Minimum Effective Concentration (MEC):**

   It is defined as the minimum concentration of drug in plasma required to produce the therapeutic effect. It reflects the minimum concentration of drug at the receptor site to elicit the desired pharmacological response.

   The concentration of drug below MEC is said to be in the sub-therapeutic level.

   In case of antibiotics, the term minimum inhibitory concentration (MIC) is used. It describes the minimum concentration of antibiotic in plasma required to kill or inhibit the growth of micro organisms.
2. Maximum Safe Concentration (MSC): Also called as *minimum toxic concentration (MTC)*. It is the concentration of drug in plasma above which adverse or unwanted effects are precipitated. Concentration of drug above MSC is said to be in the *toxic level*.

3. Onset of Action: The beginning of pharmacological response is called as *onset of action*. It occurs when the plasma drug concentration just exceeds the required MEC.

4. Onset Time: It is the time required for the drug to start producing pharmacological response. It corresponds to the time for the plasma concentration to reach MEC after administration of drug.
5. **Duration of Action**:

The time period for which the plasma concentration of drug remains above the MEC level is called as **duration of drug action**. It is also defined as the difference between onset time and time for the drug to decline back to MEC.

6. **Intensity of Action**:

It is the maximum pharmacological response produced by the peak plasma concentration of drug. It is also called as **peak response**.
7. **Therapeutic Range**: The drug concentration between MEC and MSC represents the *therapeutic range*. It is also known as *therapeutic window*.

8. **Therapeutic Index**: The ratio of MSC to MEC is called as *therapeutic index*. It is also defined as the ratio of dose required to produce toxic or lethal effects to dose required to produce therapeutic effect.