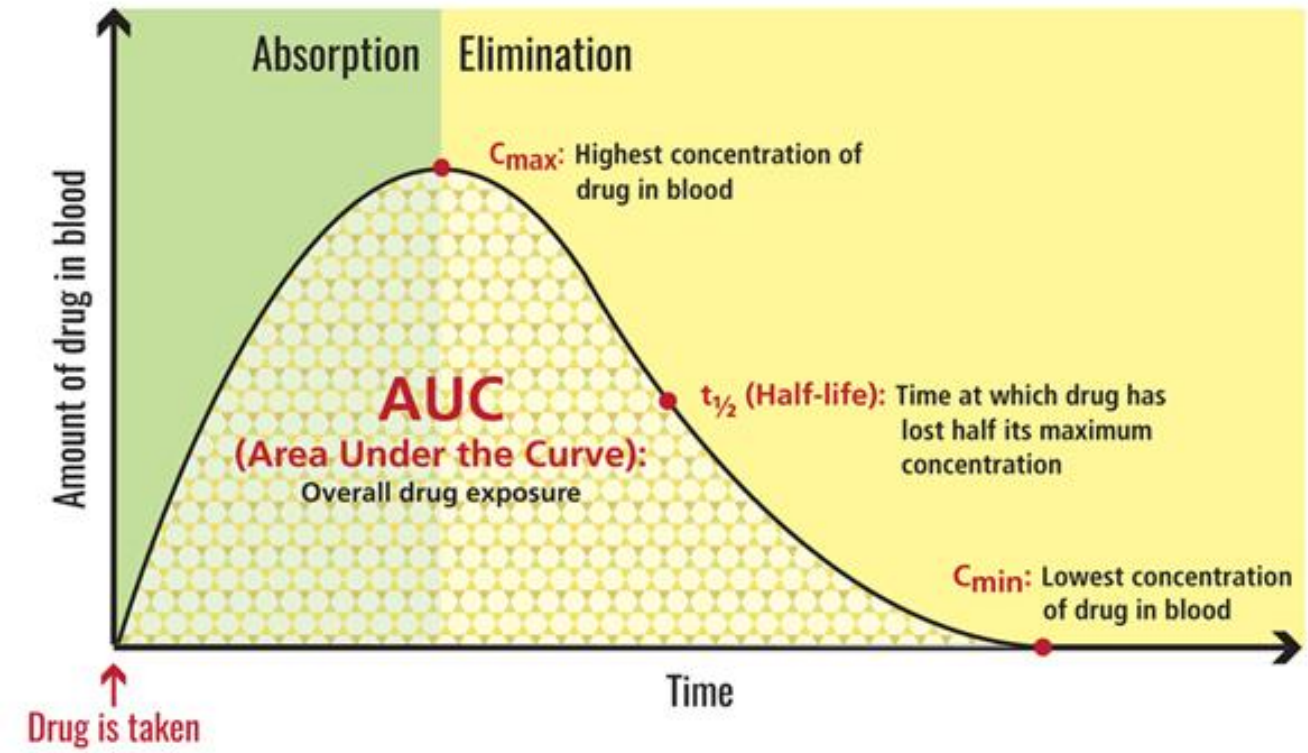

Pharmacokinetics

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Contents

- Definition and introduction to Pharmacokinetics
- Compartment models
- Non compartment models
- Physiological models

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.

- 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:

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

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

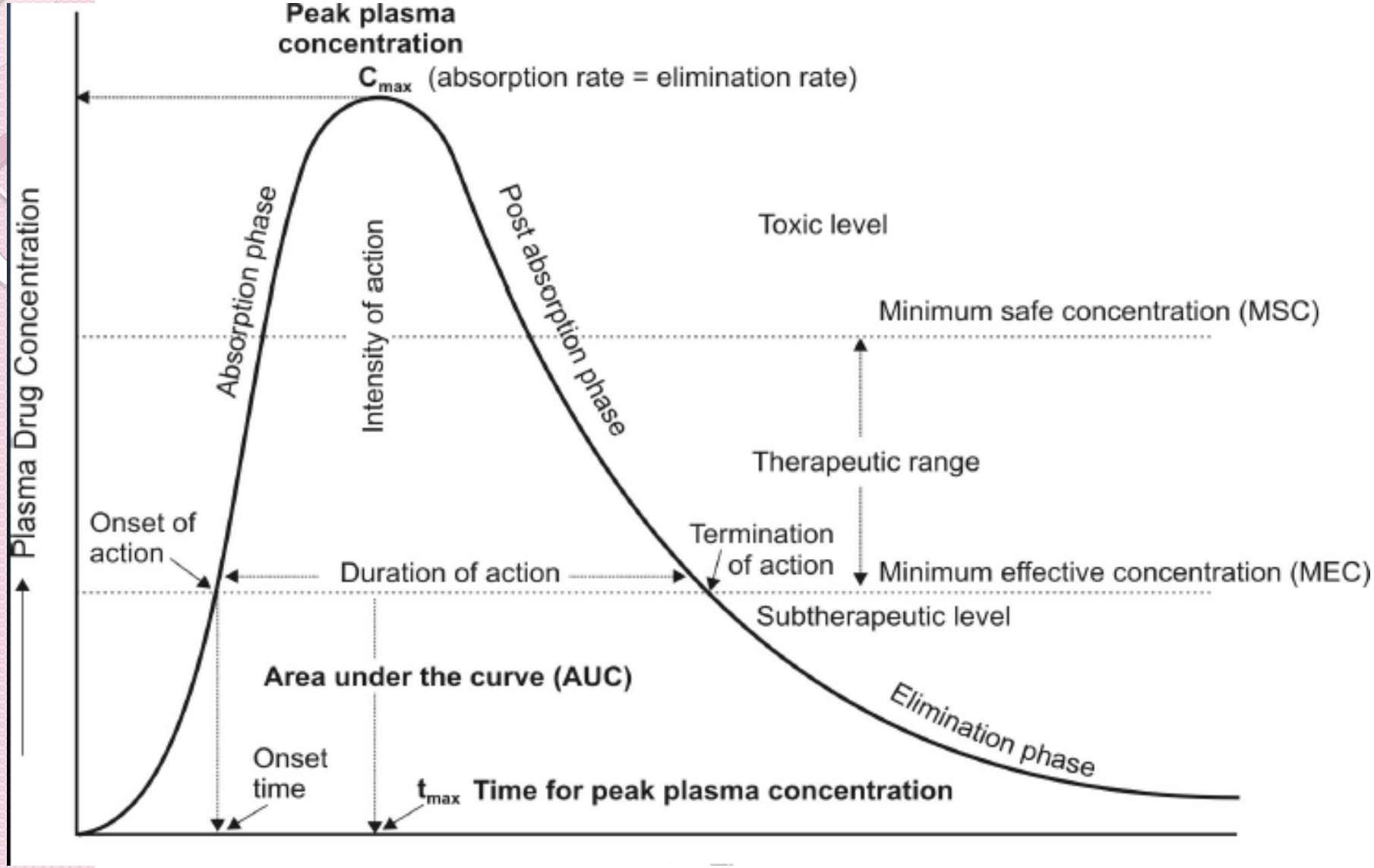
2. **Toxicokinetics** is defined as the application of pharmacokinetic principles to the design, conduct and interpretation of drug safety evaluation studies.

Plasma Drug Concentration-Time Profile

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 concentration
C_{max} (absorption rate = elimination rate)
Plasma Drug Concentration
Absorption phase
Intensity of action
Post absorption phase
Toxic level
Minimum safe concentration (MSC)
Therapeutic range
Onset of action
Termination of action
Duration of action
Minimum effective concentration (MEC)
Subtherapeutic level
Area under the curve (AUC)
Elimination phase
Onset time
t_{max} Time for peak plasma concentration

Pharmacokinetic Parameters

1. Peak Plasma Concentration (Cmax): The peak plasma level depends upon –
    - The administered dose
    - Rate of absorption, and
    - Rate of elimination
2. Time of Peak Concentration (tmax)
3. Area Under the Curve (AUC)

Pharmacodynamic Parameters

1. Minimum Effective Concentration (MEC)
2. Maximum Safe Concentration (MSC)
3. Onset of Action
4. Onset Time
5. Duration of Action
6. Intensity of Action
7. Therapeutic Range
8. Therapeutic Index

Pharmacokinetic Parameters

Three important parameters useful in assessing the bioavailability of a drug from its formulation are:

1. Peak plasma concentration (Cmax): The point at which, **maximum concentration** of drug in plasma.

Unit: µg/ml

2. Time of peak concentration (tmax): The time for the drug to reach peak concentration in plasma (after extra vascular administration).

Unit: hrs

- Useful in estimating onset of action and rate of absorption.
- Important in assessing the efficacy of single dose drugs used to treat acute conditions (pain, insomnia).

3. Area under curve (AUC): It represents *the total integrated area under the plasma level-time profile and expresses the* **total amount of the drug that comes into systemic circulation** *after its administration.*

Unit: *µg/ml x hrs*

- Represents extent of absorption – evaluating the bioavailability of drug from its dosage form.
- Important for drugs administered repetitively for treatment of chronic conditions(asthma or epilepsy).

Pharmacodynamic parameters

1. Minimum effective concentration (MEC): Minimum concentration of drug in plasma/receptor site required to produce therapeutic effect.
- Concentration below MEC – **sub therapeutic level**
- Antibiotics – MIC

2. Maximum safe concentration (MSC): Concentration in plasma above which adverse or unwanted effects are precipitated.
- Concentration above MSC – **toxic level**

3. Onset time: Time required to start producing pharmacological response. Time for plasma concentration to reach MEC after administrating drug

4. Onset of action: The beginning of pharmacologic response. It occurs when plasma drug concentration just exceeds the required MEC.

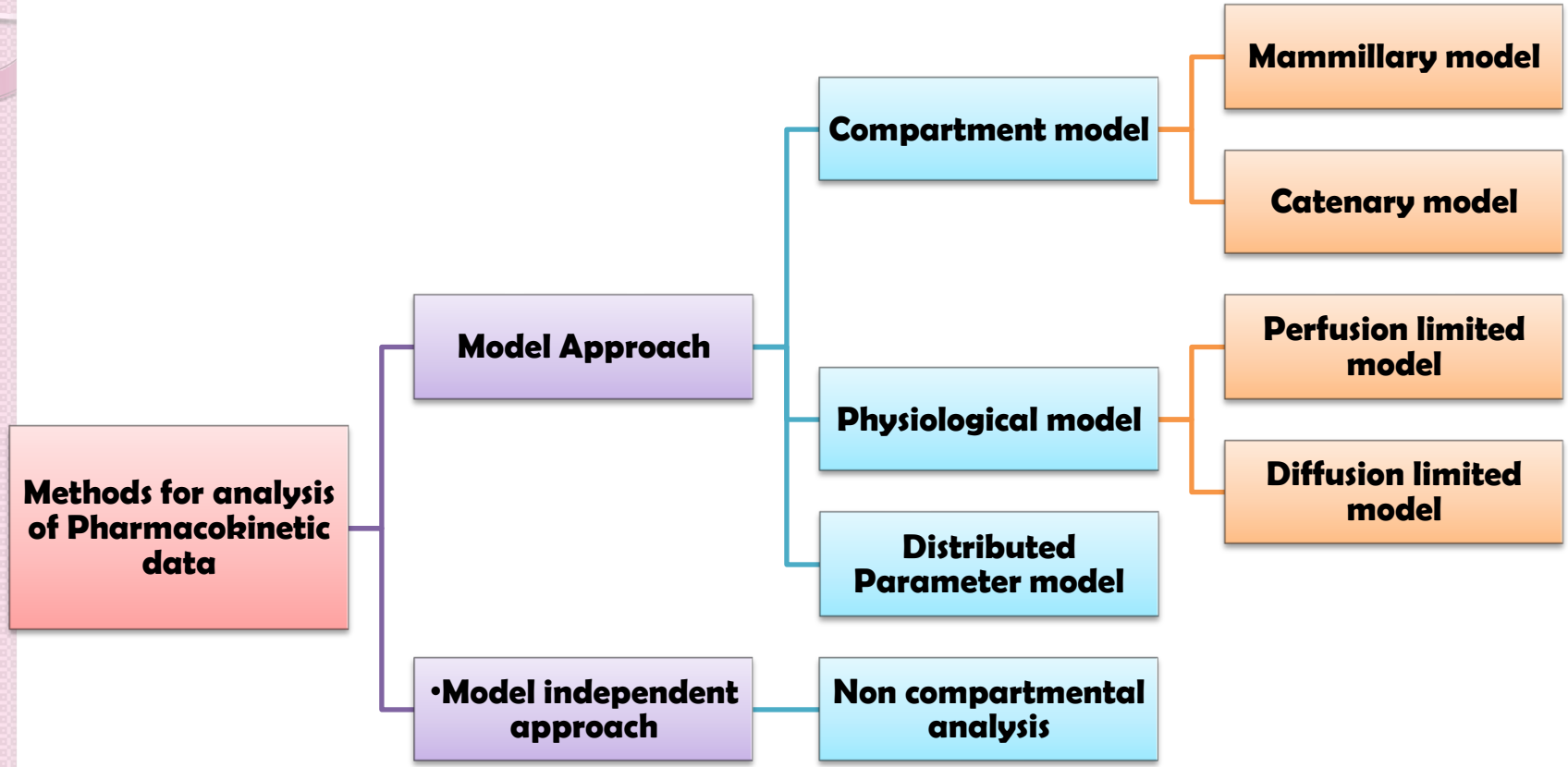
5. Duration of action: The time period for which the plasma concentration of drug remains above MEC level.

6. Intensity of action: It is the minimum pharmacologic response produced by the peak plasma conc. of drug.

7. Therapeutic range : The drug conc. between MEC and MSC

8. Therapeutic index: The ratio of maximum safe concentration to minimum effective concentration of the drug is called as the therapeutic index i.e. MSC/MEC.

MATHEMATICAL ANALYSIS OF PHARMACOKINETIC DATA



Pharmacokinetic model approach

In this approach , models are used to describe changes in drug concentration with time.

A **model** is a hypothesis that employs mathematical terms to concisely describe quantitative relationships

Pharmacokinetic models are hypothetical structures that are used to describe the fate of a drug in a biological system following its administration.

A **compartment** is a group of tissues with similar blood flow and drug affinity. A compartment is not a real physiologic or anatomic region

Applications of Pharmacokinetic Models

1. Characterizing the behaviour of drugs in patients.
2. Predicting the concentration of drug in various body fluids with any dosage regimen.
3. Predicting the multiple-dose concentration curves from single dose experiments.
4. Calculating the optimum dosage regimen for individual patients.
5. Evaluating the risk of toxicity with certain dosage regimens.
6. Correlating plasma drug concentration with pharmacological response.
7. Evaluating the bioequivalence/bioinequivalence between different formulations of the same drug.
8. Estimating the possibility of drug and/or metabolite(s) accumulation in the body.
9. Determining the influence of altered physiology/disease state on drug ADME.
10. Explaining drug interactions.

•Types of Pharmacokinetic Models

Pharmacokinetic models are of three different types –

a.Compartment models – are also called as *empirical models,* and

b.Physiological models – are *realistic models.*

c.Distributed parameter models – are also *realistic models.*

a.Compartment Models

Compartmental analysis is the traditional and most commonly used approach to pharmacokinetic characterization of a drug. These models simply interpolate the experimental data and allow an *empirical formula* to estimate the drug concentration with time. The body is divided into hypothetical compartments arranged either in series or parallel to each other, communicating with each other. These compartments are virtual and is considered as tissue or group of tissues that have similar drug distribution characteristics i.e. similar blood flow and affinity.

Depending upon whether the compartments are arranged parallel or in a series, compartment models are divided into two categories —

1. Mammillary model
2. Catenary model.

Since compartments are hypothetical in nature, compartment models are based on certain *assumptions* –

1. The body is represented as a series of compartments arranged either in series or parallel to each other, that communicate reversibly with each other.
2. Each compartment is not a real physiologic or anatomic region but a fictitious or virtual one and considered as a tissue or group of tissues that have similar drug distribution characteristics (similar blood flow and affinity). This assumption is necessary because if every organ, tissue or body fluid that can get equilibrated with the drug is considered as a separate compartment, the body will comprise of infinite number of compartments and mathematical description of such a model will be too complex.
3. Within each compartment, the drug is considered to be rapidly and uniformly distributed i.e. the compartment is well-stirred.
4. The rate of drug movement between compartments (i.e. entry and exit) is described by first-order kinetics.
5. Rate constants are used to represent rate of entry into and exit from the compartment.

ADVANTAGES AND APPLICATIONS

- Simple and flexible approach
- Gives visual representation of various rate processes involved in drug disposition.
- Possible to derive equations describing drug concentration changes in each compartment.
- One can estimate the amount of drug in any compartment of the system after drug is introduced into a given compartment.
- Important in development of dosage regimens.
- Drug data comparison can be done using this model .
- Useful in predicting plasma drug concentration time profile both in normal physiological and pathological condition.
- Enables monitoring of drug concentration change with time with limited amount of data.

DISADVANTAGES

- Drug given by IV route may behave according to single compartment model but the same drug given by oral route may show 2 compartment behavior.
- The type of compartment behavior i.e. Type of compartment model may change with the route of administration.
- Extensive efforts are required to design an exact model that correctly predicts the ADME of a drug.
- The model may vary within a study population.
- Difficulties arise when models are used to interpret the difference between results from human and animal experiments.
- Data fitting is required.

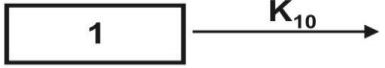
1. **Mammillary Model** - It is the most common model. In this model the central compartment is connected parallel to one or more peripheral compartment. The central compartment has high vascularity and high perfusion like lungs, liver, kidneys. Elimination also occurs through these compartments in most cases. The peripheral compartments or tissue compartment or compartment denoted by numbers 2,3,4...etc have low vascularity and poor perfusion. Movements of drugs between the compartment follows first order kinetics.[Note-K12 denotes the drug movement from compartment one to compartment two or from central compartment to one of the peripheral compartment.]

The number of rate constants which will appear in a particular compartment model is given by R.
For intravenous administration, $R = 2n - 1$
For extravascular administration, $R = 2n$
where n = number of compartments.

"OPEN" and "CLOSED" models:

- The term "open" itself mean that, the administered drug dose is removed from body by an excretory mechanism (for most drugs, organs of excretion of drug is kidney)
- If the drug is not removed from the body then model refers as "closed" model

Model 1

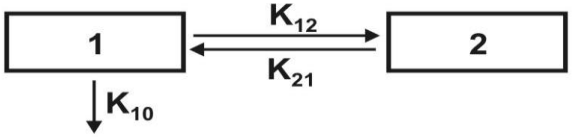


One-compartment open model, intravenous administration

Model 2

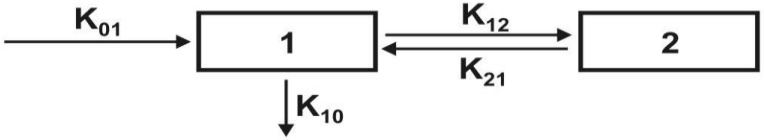
One-compartment open model, extravascular (oral, rectal, etc.) administration

Model 3



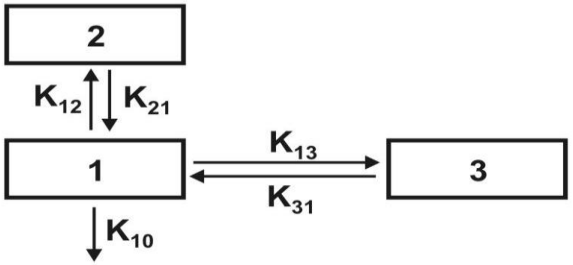
Two-compartment open model, intravenous administration

Model 4



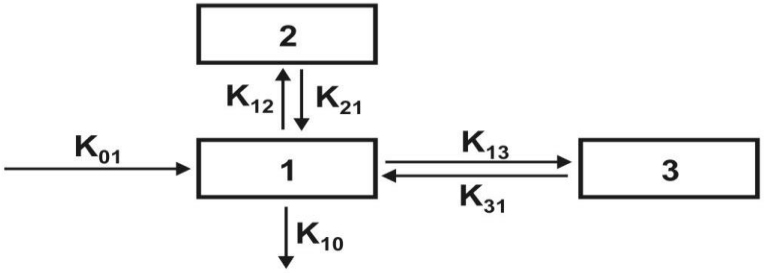
Two-compartment open model, extravascular administration

Model 5



Three-compartment open model, intravenous administration

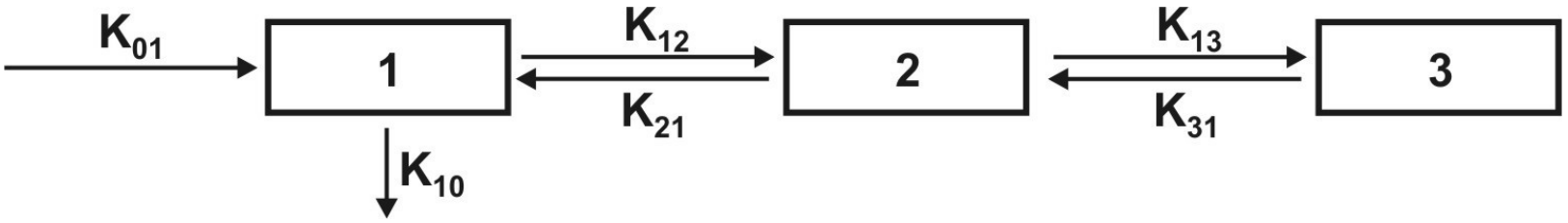
Model 6



Three-compartment open model, extravascular administration

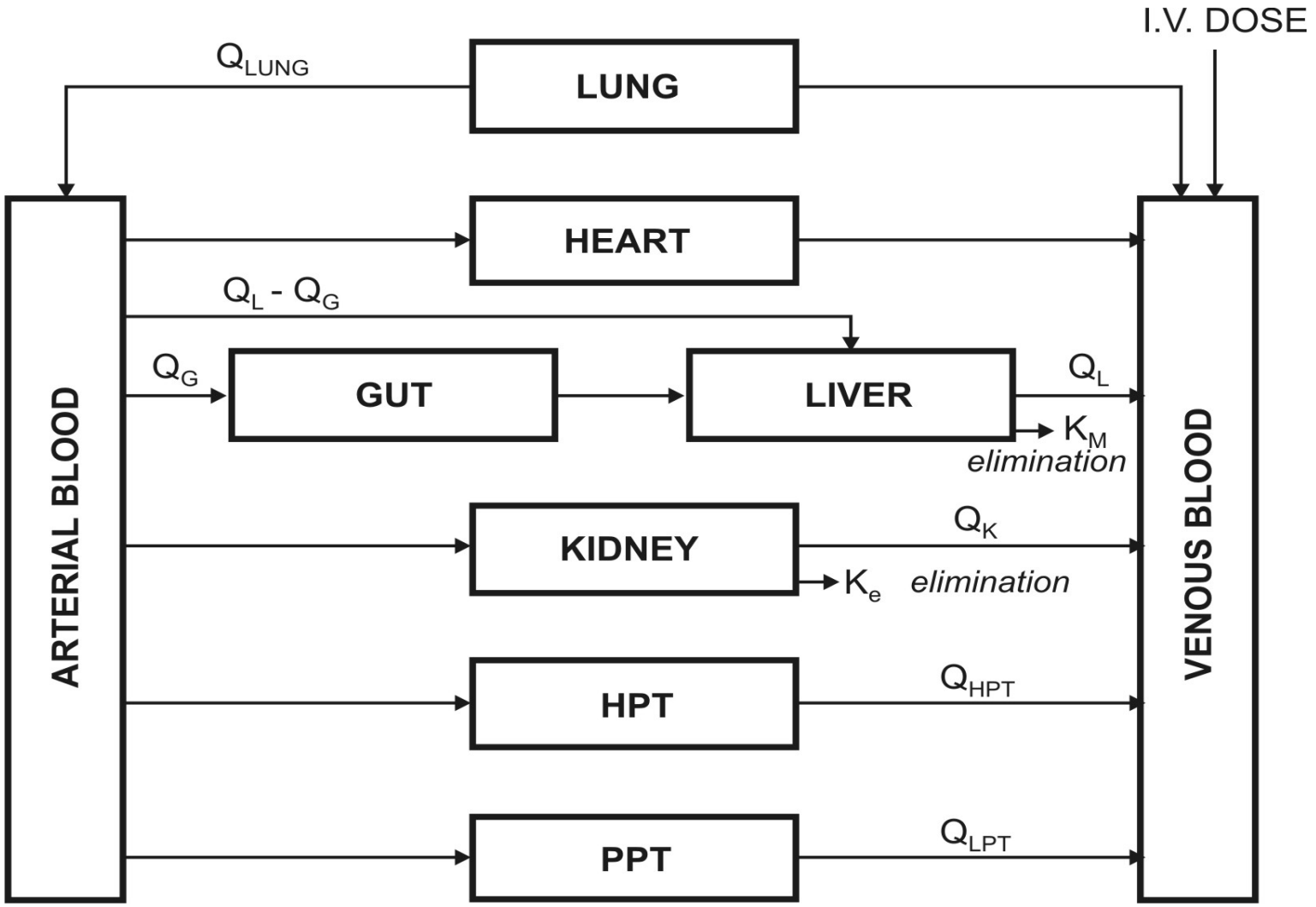
2. Catenary Model – In catenary model the compartments are joined in series.

This model is rarely used.



b. Physiological Models

- These models are also known as *physiologically-based pharmacokinetic models* (***PB-PK models***).
- They are drawn on the basis of known anatomic and physiological data and thus present a more realistic picture of drug disposition in various organs and tissues.
- The number of compartments to be included in the model depends upon the disposition characteristics of the drug.
- Organs with similar perfusion is grouped in a single compartment, like lungs, liver, brain and kidney are grouped as rapidly equilibrating tissues (RET) while muscles and adipose as slowly equilibrating tissues (SET).
- Organs or tissues such as bones that have no drug penetration are excluded.



The term Q indicates rate of blood flow to a body region;
HPT indicates highly perfused tissue
PPT indicates poorly perfused tissue
Km and Ke are first order rate constant for hepatic elimination & urinary excretion resp.

ADVANTAGES

- Mathematical approach is straightforward
- The model is suitable if tissue drug concentration and binding is known
- The model gives exact description of plasma drug concentration time profile in any organ or tissue.
- Data fitting is not required.
- Easy to explain ADME mechanism of a drug.
- The influence of altered physiology or pathology on drug disposition can be easily predicted.

DISADVANTAGES

- Obtaining experimental data is a exhaustive process.

The physiological models are further categorized into two types –

1. Blood flow rate-limited models – These models are more popular and commonly used than the second type, and are based on the assumption that the drug movement within a body region is much more rapid than its rate of delivery to that region by the perfusing blood. These models are therefore also called as *perfusion rate-limited models*. This assumption is however applicable only to the highly membrane permeable drugs i.e. low molecular weight, poorly ionised and highly lipophilic drugs, for example, thiopental, lidocaine, etc.

2. Membrane permeation rate-limited models – These models are more complex and applicable to highly polar, ionised and charged drugs, in which case the cell membrane acts as a barrier for the drug that gradually permeates by diffusion. These models are therefore also called as *diffusion-limited models*.

c. Distributed parameter model - This model is analogous to physiological model. This model is specifically useful for assessing regional differences in drug concentrations in tumours or necrotic tissues.

Difference between compartment and physiological modelling

Compartment modelling	Physiological modelling
Hypothetical approach	Realistic approach
Experimentally simple	Experimentally difficult
It is often used –"first model"	Less commonly used owing to its complexicity
Complex mathematical treatment is necessary	Mathematical treatment is straight forward
Data fitting is required	Data fitting is not necessary
Used when there is little information about the tiisues	Used where tissue drug concentration and binding are known
Extrapolation of animal data to humans is not possible	Extrapolation of animal data to humans is easy
ADME Mechanism cannot be explained	Easy to explain ADME Mechanism
Frequently used for data comparison of various drugs	Less commonly used for data comparison.
Effect of pathological conditions on drug ADME cannot be determined.	Effect of pathological conditions on drug ADME can be determined.

Noncompartmental Analysis

- The ***noncompartmental analysis***, also called as the ***model-independent method***, does not require the assumption of specific compartment model.
- This method is, however, *based on the assumption that the drugs or metabolites follow linear kinetics,* and on this basis, this technique can be applied to any compartment model.
- *The noncompartmental approach, based on the* ***statistical moments theory***, involves collection of experimental data following a single dose of drug.
- If one considers the time course of drug concentration in plasma as a statistical distribution curve, then:

MRT = AUMC/AUC

where MRT = mean residence time

AUMC = area under the *first-moment curve*

AUC = area under the *zero-moment curve*

MRT *is defined as the average amount of time spent by the drug in the body before being eliminated.*

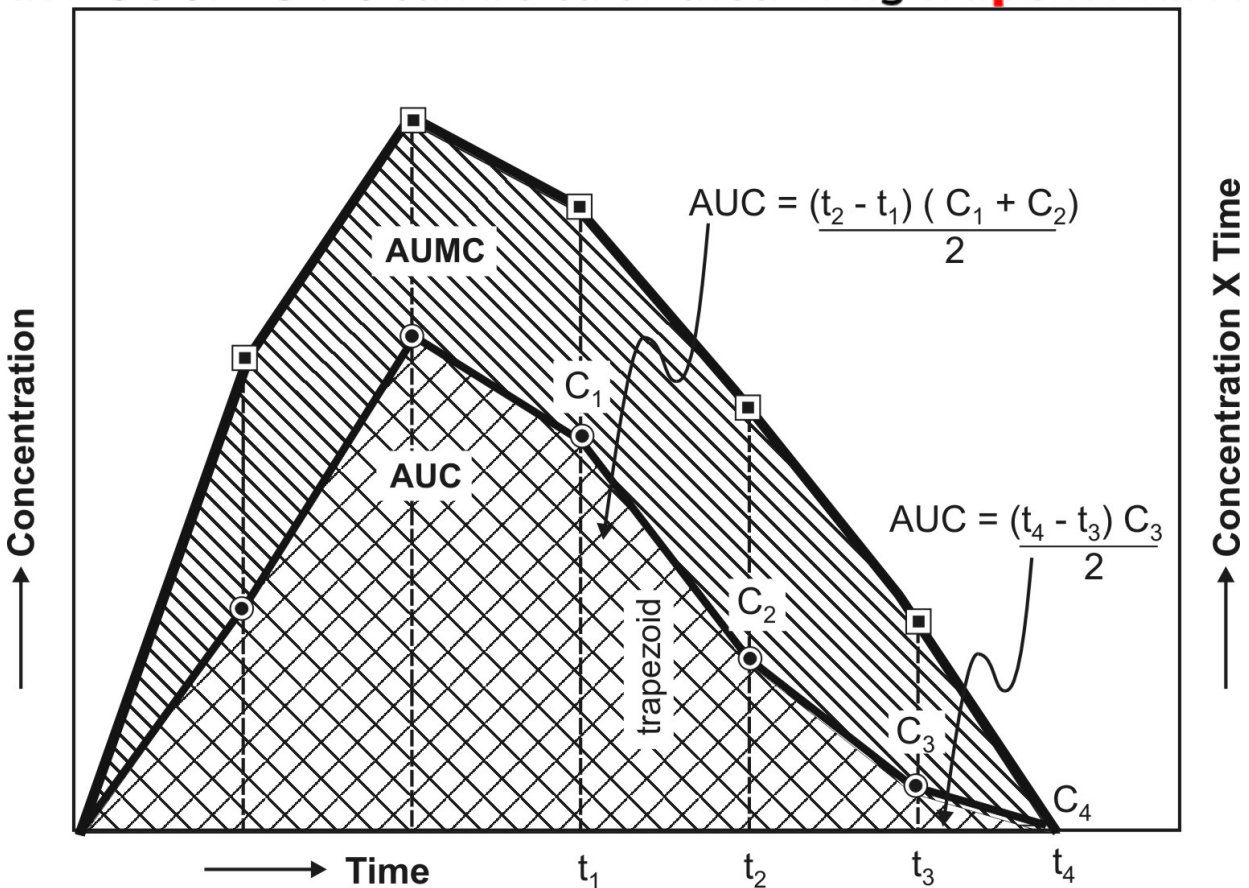
- **AUMC** is obtained by the plot of product of plasma drug concentration and time vs time i.e. **C.t vs t**

$$AUMC = \int_0^\infty C\,t\,dt$$

- **AUC** is obtained by plotting **C vs t.**

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

- Both AUC & AUMC can be calculated using **trapezoidal rule.**



Application of Model Independent / Noncompartmental Model-

- It is used to estimate the important pharmacokinetic parameters like bioavailability, clearance and apparent volume of distribution.
- It is used in determining half life, rate of absorption and first order absorption rate constant of the drug.

Advantages :

- Ease of derivation of pharmacokinetic parameters
- Same mathematical treatment can be applied to almost any drug or metabolite provided they follow first order kinetics
- Drug disposition characteristics information is not required.

Disadvantages :

- It provides limited information regarding plasma drug concentration time profile.
- It does not treat non-linear cases


Thank
you