UNIT

XV

PHARMACOKINETIC MODELS

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INTRODUCTION

The transport of drugs through the body is a complicated process. Two key approaches have been presented to provide a standardised and easy approach to define, analyse, and interpret data obtained during in-vivo drug disposal research.

1. Model-based approach and
2. Model-free approach (also called as non-compartmental analysis).

MODEL BASED APPROACH FOR PHARMACOKINETIC DATA ANALYSIS

Models are employed in this method to describe changes in drug concentration in the body over time.

Pharmacokinetic Models Types: There are three types of pharmacokinetic models:

1. Compartment models, also known as empirical models
2. Physiological models are accurate simulations.
3. Models with distributed parameters are also realistic

COMPARTMENT MODELS

The most popular method for pharmacokinetic characterisation of a medication is compartmental analysis. Compartment is a **kinetically distinguishable** pool of organs or tissues. When **rate of administration** and **rate of excetion** of a drug is same in different organs, then those organs grouped into same compartment. Compartment models are based on Because compartments are unpredictable, particular assumptions must be made.

1. The body is depicted as a series of compartments that are placed in either a series or parallel fashion.
2. Each compartment is a virtual representation of a true physiologic or anatomic location.

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3. A tissue or a set of tissues with comparable medication distribution properties (similar blood flow and affinity) together in one compartment.
4. The drug is thought to be distributed quickly and uniformly throughout each compartment.
5. First-order kinetics describes the rate of drug transport between compartments (i.e. entry and exit).

Compartment models are classified into two groups based on whether the compartments are arranged parallel or in a series:

1. Mammillary model
2. Catenary model.

1. Mammillary Model

The most popular compartment model is this one. There are one or more peripheral compartments in it or tissue compartments (low vascularity and poorly perfused organ**)** a connection to the main compartment (highly perfused tissues) in the same way as satellites are connected to a planet (i.e., they are joined parallel to the central compartment). The drug is directly absorbed or eliminated from central compartment.

i. **One-compartment Model:** Only one compartment exist which receive drug either directly (after i.v. administration) or by absorption (after e.g. administration) very fast.

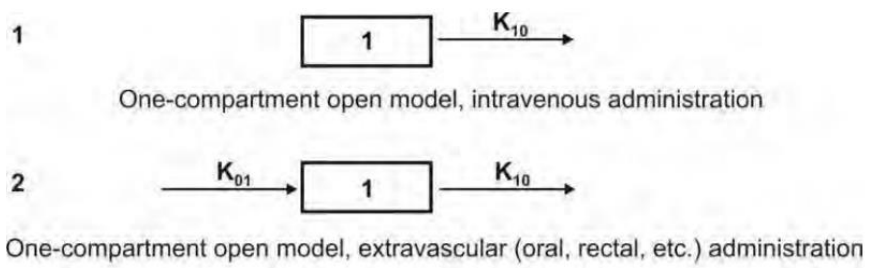

Figure 15.1: Block diagram showing the movement of drug in a one-compartment open model

ii. **Two-compartment Model:** Here, body is divided virtually into two compartments, i.e. **central compartment** (plasma and tissues with

significant blood flow, such as the lungs, liver, and kidneys- denoted by #1) and **peripheral compartment** (such as muscle, adipose tissue, bones etc.- denoted by #2).

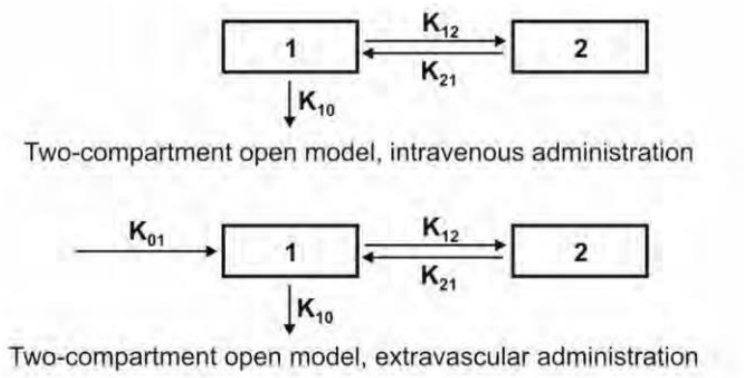

Figure 15.2: Block diagram showing the movement of drug in a two-compartment open model

iii. Three-compartment Model:

a) Central Compartment (1): highly perfused—e.g. Blood/plasma & highly perfused organs

b) Peripheral Compartment (2): less perfused—e.g. Muscle

c) Peripheral Compartment (3): still less perfused—e.g. Bones

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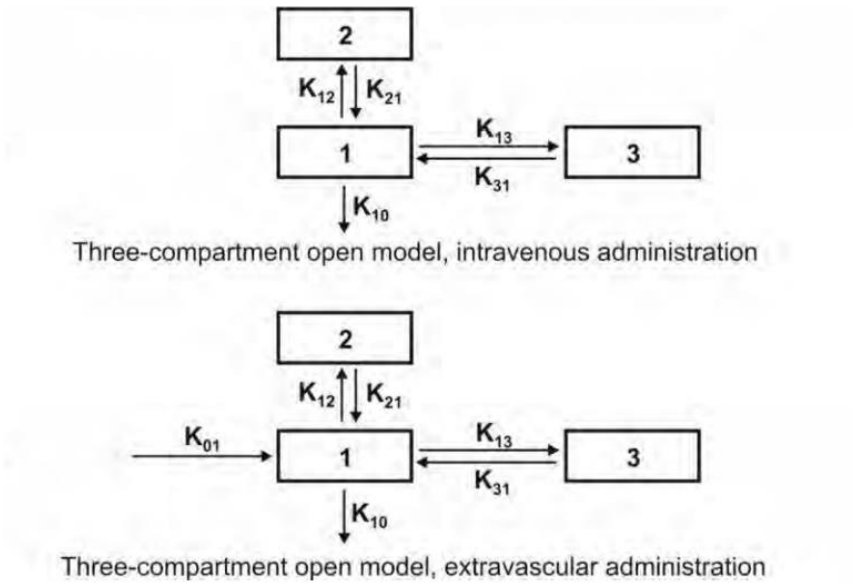

Figure 15.3: Block diagram showing the movement of drug in a three-compartment open model

2. Catenary Model

The compartments in this model are connected in a sequence, much like train compartments. The numerous organs are directly related to the blood compartment; hence this is not evident medically or physically. As a result, this model is rarely employed.

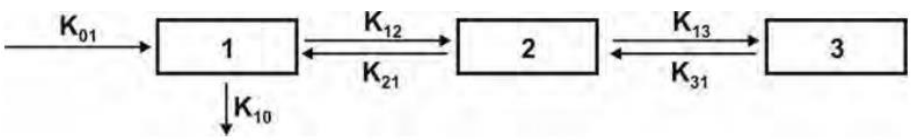

Figure 15.4: Block diagram showing the movement of drug in a Catenary model

The compartment modelling method offers a number of advantages and applications:

1. It is a simple and flexible method that is commonly utilized.
2. It depicts the many rate processes involved in drug disposition visually.

3. It demonstrates the number of rate constants required to explain these processes.
4. It allows for limited data monitoring of medication concentration changes over time.
5. It can be used to forecast medication concentration-time profiles.
6. It is crucial in the formulation of dose regimens.

Limitations: The following are some disadvantages of compartment modelling:

1. The compartments have no relevance to the species' physiological functions or anatomic structure.
2. Developing a precise model necessitates considerable work.
3. Within a study population, the model may differ.
4. The method can only be used on a single substance under investigation.
5. Depending on the method of administration, drug behaviour within the body may fit into several compartmental models.

Physiological Models = Pharmacokinetic models based on physiological data (PB-PK models)

They are based on anatomic and physiological data and so provide a more accurate picture of medication distribution in diverse organs and tissues. Organs or tissues with no drug penetration, such as bones, are not included. Organs of major importance (liver, lungs, kidney etc) in drug absorption are considered separately. Other tissues with similar perfusion qualities are classified as RET (rapidly equilibrating tissue), whereas muscles and adipose are classified as slowly equilibrating tissues (SET). Physiologically, rather than mathematically, the size or mass of each tissue compartment is determined. The ability of the tissue to accumulate drug as well as the rate of blood perfusion to the tissue, indicated by Q, dictate the drug concentration in the tissue. In this flow diagram, compartments are placed in a series.

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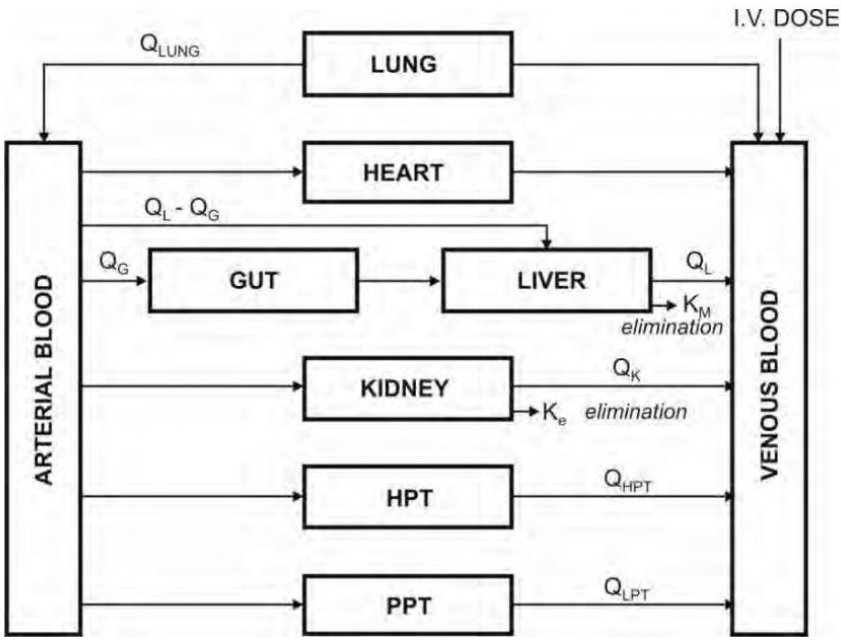

Figure 15.5: Block diagram showing the movement of drug in a physiological model

The term Q refers to the rate of blood flow to a specific bodily part. PPT stands for poorly perfused tissues, while HPT is for other highly perfused tissues. For hepatic elimination, Km is the rate constant, while for urine excretion, K_e is the first-order rate constant.

The physiological models are divided into two categories:

a) **Blood flow rate-limited models–** These models are based on the premise that drug movement inside a body region is significantly faster than the rate of blood delivery to that location. As a result, these models are often known as perfusion rate-limited models.

b) **Membrane permeation rate-limited models –**These models are more sophisticated and apply to highly polar, ionized, and charged medicines, in which the cell membrane functions as a barrier for the drug, which diffuses through the cell. As a result, these models are often known as diffusion-limited models.

Advantages of Physiological modelling over the conventional compartment modelling:

1. The mathematical approach is simple.
2. When the concentration and binding of tissue drugs are known, the model works well.
3. In any organ or tissue, the model accurately describes the drug concentration-time profile.
4. Drug disposition can be predicted easily when physiology or pathophysiology is altered.
5. This model can simply explain the mechanism of the drug's ADME.

Disadvantages of physiological modelling include:

1. Gathering experimental data is a time-consuming operation.
2. Because most physiological models use an average blood flow for individual participants, personalized dose prediction is challenging.
3. The number of data points is insufficient to estimate the pharmacokinetic characteristics.
4. Monitoring drug concentrations in the body is difficult due to the large amount of data required.

DISTRIBUTED PARAMETER MODEL

This model is similar to a physiological model, however it was created to account for:

- Variations in blood flow to an organ; and
- Variations in drug diffusion in an organ.

As a result, a model like this can be used to examine regional changes in medication concentrations in tumours or necrotic tissues.

The mathematical equations in the distributed parameter model are more complex than those in physiological models, and collecting drug concentration data is more difficult.

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Non-compartmental Analysis = Model-independent method for pharmacokinetic data analysis

This strategy does not necessitate the use of a compartment model. This method, on the other hand, is based on the assumption that medications or metabolites have linear kinetics, and may thus be applied to any compartment model.

The non-compartmental technique, which is based on statistical moments theory, collects experimental data after a single pharmacological dose. If the time course of drug concentration in plasma is seen as a statistical distribution curve, the following results are obtained as:

$$MRT = \frac{AUMC}{AUC} = \frac{\int_0^\infty C.t \times dt}{\int_0^\infty C \times dt}$$
$$= \frac{total\ residence\ time\ for\ all\ drug\ molecules\ in\ body}{total\ number\ of\ drug\ molecules}$$

Where, MRT = mean residence time

AUMC = area under the first-moment curve

AUC = area under the zero-moment curve

A plot of the product of plasma drug concentration and time (i.e., C.t) vs time t from zero to infinity yields the AUMC. It can be stated mathematically as follows:

AMUC = $\int_0^\infty C.t \times dt$

AUC is calculated by plotting plasma drug concentration against time from 0 to infinity. It can be stated mathematically as follows:

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

The trapezoidal rule can be used to compute the AUMC and AUC from the appropriate graphs:

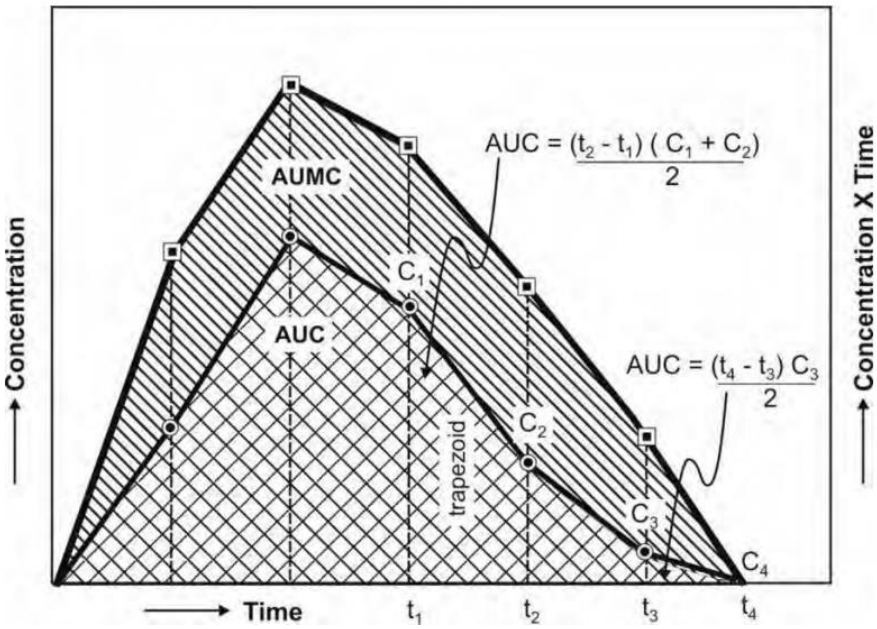

Figure 15.6: Calculation of AUC and AUMC in a model-independent method for pharmacokinetic data analysis

Mean Residence Time (MRT): The average period of time a drug spends in the body before being removed is known as MRT. MRT stands for the time it takes for 63.2 percent of an intravenous bolus dosage to be removed. When the drug is given in a different way than an i.v. bolus, the readings will always be higher.

The following are some examples of non-compartmental method applications:

1. It's commonly used to calculate key pharmacokinetic characteristics like bioavailability, clearance, and apparent volume of distribution.
2. The approach can also be used to calculate the drug's half-life, rate of absorption, and first-order absorption rate constant.

The non-compartmental technique has the following advantages:

1. Easy derivation of pharmacokinetic parameters using basic algebraic equations.

2. As long as the drug or metabolite follows first-order kinetics, the same mathematical treatment can be employed.
3. There is no need for a full discussion of drug disposition features.

Disadvantages this approach has the following drawbacks:

1. It offers little information on the plasma drug concentration-time profile. It usually deals with averages.
2. Non-linear scenarios are not sufficiently addressed by the approach.