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Syeda Komal Fatima [a] Ayesha Sabir [b] Fahad Pervaiz [c]

A Deeper Insight into Pharmacokinetics of Drugs Following one Compartment Model

Abstract

This article discusses the mathematical pharmacokinetic models with reference to one open compartment model in detail. Four types of models, IV, bolus, extravascular 1st and 0 order, have been studied. Mathematical approaches to predict the pharmacokinetic parameters, including elimination half-life, rate constant and drug clearance, have been included. This article focuses on the significance of one open compartment model to study the distribution and elimination of drugs in the body beforehand, to determine whether the drugs under study should proceed to clinical trials or not. Thus, the prediction of the pharmacokinetics of the drug at an earlier stage with the help of this mathematical model saves time and cost during drug and discovery and drug development.

Key Words: One Compartment Model, Open Model, Pharmacokinetic Models, Elimination Half-Life, Drug Clearance, Elimination Rate Constant, Pharmacokinetics (PK).

Introduction

A model can simply be defined as a hypothesis that makes use of mathematical formulas to predict certain parameters and quantities. The ability of a model to predict these parameters is governed by the appropriate selection of mathematical formulas for better prediction of PK parameters. These parameters are predicted the application of the most appropriate PK model to the data available. For instance, a PK model has the potential to elucidate the drug amount in the liver 60 minutes after the extravascular (oral) administration of the drug (e.g., 20-mg dose administered). In this example, the time is the independent variable (plotted on the x-axis), and the 'C' in the liver is the dependent variable (plotted on the y-axis). By the use of time-versus-CD data, the resulting model equation can be derived to predict the liver drug concentration with respect to time. These pharmacokinetic models are derived to check the rate processes of the drug's pharmacokinetics; absorption, distribution, and elimination, which is a result, predicts the concentrations of the drug.

Uses of PK Models

i. Predict concentration in plasma, urine and different body tissues.
ii. Predict probable accumulation of drugs & their various metabolites.
iii. To relate the level to drugs in the body with the resulting toxicologic activity.
iv. Calculate bioequivalence.
v. Elucidate the changes in the body's physiology or how a present disease affects the pharmacokinetic process.
vi. To explain the unrequired interactions between different drugs.
vii. To calculate the most appropriate dosage regimen for each patient.
viii. It is with the help of these PK models that the dosage regimen of certain drugs has been modified to be more efficacious and less toxic. One such example is that of Gentamicin; in the past multiple doses per day were

[a] Undergraduate Student, Department of Pharmaceutics, Faculty of Pharmacy, Islamia University Bahawalpur, Bahawalpur, Punjab, Pakistan.
[b] Undergraduate Student, Department of Pharmaceutics, Faculty of Pharmacy, Islamia University Bahawalpur, Bahawalpur, Punjab, Pakistan.
[c] Associate Professor, Department of Pharmaceutics, Faculty of Pharmacy, Islamia University Bahawalpur, Bahawalpur, Punjab, Pakistan. Email: fahad.pervaiz@iub.edu.pk

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suggested, which proved to be less efficacious and more toxic, but PK models have suggested that the administration of a single dose of Gentamicin per day will not only lead to a better safety profile but also improved clinical outcome.

ix. Also describe urea kinetics in and between hemodialysis.

Assumptions of Compartment Model

- Streamlining presumptions used in PK models to depict a framework regarding the pharmacodynamics of medications inside the human body. For instance, most of the PK models expect that the Cp levels (drug level in plasma) are similar to the entire drug level inside the body. (Ahmed & Applications, 2015)
- Models might be classified physiologically, observationally, or on the basis of compartments involved. The model that basically introduces the information and permits experimental equation in order to appraise drug concentration after some period is defended in case restricted data are free. Experimental models are reasonable yet not valuable in clarifying the component of the genuine interaction through which the drug understudy is distributed and excreted in the body (Avent, Rogers, Cheng, & Paterson, 2011).
- Models that are physiologically based models have certain concerning hindrances. Using this model, and isolated from the requirement to test out the tissue and screen out the circulation system to the liver in vivo, the clinician needs to appreciate the going with requests. What is the clinical consequence of liver medication Cp? Should Cp in the blood inside the tissue be resolved and deducted from drug concentration in the hepatic tissue?
- A basic and helpful instrument in PK is models based on the number of hypothetical compartments. For instance, expect medication is administered via IV; it dissolves quickly in the body liquids. One PK model that can portray the present circumstance is a tank containing a volume of liquid that is quickly equilibrated with the medication (Brahmankar & Jaiswal, 2005). The grouping of the medication in the tank after a given portion is represented by two boundaries:

Rate of Elimination

As the one-compartment open model hypothesizes the body as one compartment from which the drug may leave or enter, this one compartment is referred to as a 'tank', this model will assume the tank as one compartment and the distribution and elimination of the drug in this tank will be studied, and from this further, the PK parameters will be calculated. These pharmacokinetic parameters will then give the value of elimination rate of the drug per unit time that will be useful to develop the dosage regimen and the frequency with which the drug should be administered (Carleton, Kelly, Anderson-Sprecher, & del Rio, 2008).

The Volume of Distribution

The liquid volume of the tank that will dilute the drug relating to the blood and plasma through which a drug is distributed (Egbelowo & Applications).

Types of Models

Mammillary Model

A compartmental model gives a basic method of collecting entire tissues to formulate one or more compartments (Fernández-Varón et al., 2005). It is of two main types, mammillary and catenary. The mammillary model is an emphatically associated framework since one can appraise the measure of medication in any compartment of the framework after the medication is brought into a given compartment. In the one-compartment model, the drug is both added to and dispensed with from a focal compartment (Funatogawa, Funatogawa, & Yafune, 2007).

Catenary Model

It is the second most popular PK model after mammillary model (Marsot, Boulamery, Bruguerolle, & Simon,
2012). Basically, it is composed of compartments, the central compartment being the plasma, and peripheral compartments are organs. It is not preferred to the mammillary model as it does not deduce results close to the physiology of the body compared to the mammillary models and the results are not 100% reliable.

Applications of Compartment Models

i. Physiological PK models are used in the case when the tissue drug concentration and

binding are already known. They are based on realistic body tissues and blood flow.

ii. They are also used in predicting drug distribution in animals due to readily available tissues. Due to ethical regulations in experimentations, the availability of human tissues is not abundant, hence in this case, the physiological model will be a hypothetical one, in which the average blood flow found practically will be used for all individuals.

iii. It mainly depends on the physicochemical properties of the drug, whether it should be studied in a one-compartment model or a two-compartment model. E.g. drugs that dissolve rapidly in the body are always studied in a one-compartment open model.

iv. Mixing of the drug in each compartment is uniform and fast, considered as "well-stirred".

v. The overall distribution of a drug between compartments is predicted by a mathematical erm known as "rate constants".

vi. Compartment models apply linear differential equations.

One Compartment Open Model

Introduction

i. PK parameters, including distribution & elimination of the drug, are conveniently described by this process.

ii. The drug travels quickly in and out of this compartment.

iii. It is the simplest PK model.

iv. The drug may enter or exit the body (hence called open), and the body acts like a single, uniform compartment.

v. IV bolus is the simplest route of drug administration studied in this model.

vi. In this model, the drug is administered via injection all at once into a compartment & it will distribute rapidly.

vii. Only applicable to rapidly distributing drugs.

viii. In the case of IV bolus, the process of elimination will start after administration immediately.

ix. Absorption rate> Elimination rate. These can be attributed to 'input' and 'output' rates.

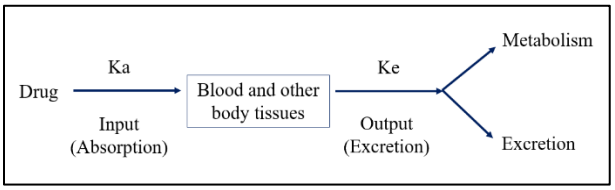

Figure 1: Absorption & Elimination Phase

Classification of One Compartment Open Model

This classification varies on the basis of difference in the route and rate of administration of the drug.

1. IV bolus.
2. Continuous IV infusion.
3. Extravascular zero-order absorption.
4. Extravascular first-order absorption.

IV Bolus Administration

When a drug that distributes in the body is given in the form of lipid intravenous injections, it takes about 2 to 3 minutes for complete circulation.

The following figure represents the administration and elimination of a drug administered via IV (bolus) that follows one open compartment model.

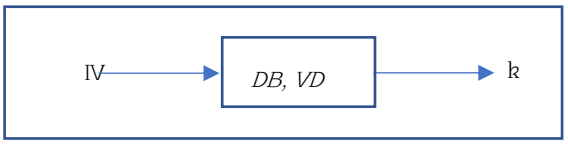

Figure 2: Pharmacokinetic Model for a Drug Administered by IV Injection

Where,
DB= amount of drug
VD= volume of distribution
ke=elimination rate constant (output)

General Equations for Rate of Drug Expression

A number of mathematical formulas are used to explain the pharmacokinetic processes in the one compartment model. (Rosenbaum, Textbook, & Simulations, 2016)

a) This formula presents the rate of change of drug in the body:

$$\frac{dx}{dt} = rate\ in - rate\ out$$

b) Absorption is very rapid in IV bolus, and the rate of change of absorption is zero, so the above equation becomes:

$$\frac{dx}{dt} = -rate\ out$$

c) Rate of drug change in IV bolus in case of first-order elimination

$$\frac{dx}{dt} = -KEX$$

Where,

KE=first-order elimination rate constant

X= amount of drug in body

Negative sign is to show elimination of drug.

Estimation of PK Parameters

Pharmacokinetic Parameters

1. Elimination half-life (t½)
2. Elimination rate constant (ke)
3. Apparent volume of distribution (Vd)
4. Clearance (Cl)

Elimination Half-Life (t½)

It is defined as

*"The time is taken for the amount of drug in the body as well as plasma concentration to decline by **one half** of 50% its initial value."*

The formula of half-life for first-order kinetics:

$$t1/2 = 0.693/k$$

Elimination Rate Constant (k)

Most drugs follow the first order elimination process, meaning that the elimination rate K at any point depends on the initial concentration of the drug. Unit used is h^{-1}And denoted by the symbol k. Drug administered via IV bolus enters the blood, referred to as the **vascular compartment.** Elimination of a drug from the body is dependent on its metabolism, tissue binding, plasma protein binding, & excretion.

- The elimination rate constant denotes the summation of these processes as shown in the given formula:

  k=km+ke

Where,

km = rate constant of metabolism

ke = rate constant of excretion

- For several routes of elimination of drug, each of these processes has its own first-order rate constant for given drug ***DB*** in the body at a given time ***t.***

$$\frac{dDB}{dt} = kDB$$

- Apply integration on the above equation to deduce:

$$DB = DB_B^0 e^{-kt} \qquad logDB = -kt/2.3 + logDB^0$$

Where, DB^0 =amount of drug in the body at 0 minutes.

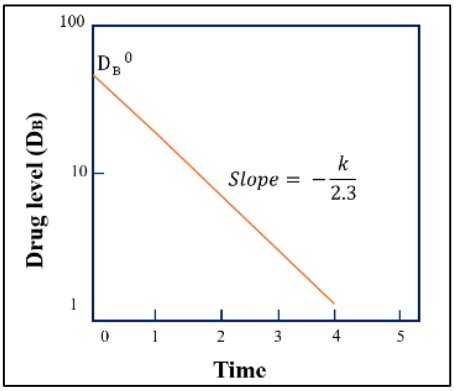

Figure 3: Semi log graph of the rate of drug elimination (Savic, Jonker, Kerbusch, Karlsson, & pharmacodynamics, 2007)

Apparent Volume of Distribution

It is defined as,

"A measure of the extent of distribution of drug and is expressed in litres."

$$\text{Vd} = \frac{\text{Dose of drug administered}}{\text{Plasma drug concentration(Cp)}}$$

Calculating the Volume of Distribution

The following formula is used to calculate Vd:

$$VD = Dose/Cp^0 = DB^0/Cp^0$$

Where,

Cp^0 represents the instantaneous CD after drug equilibration, when time 't' is 0 (time of administration).

Significance of Apparent Volume of Distribution

i. It gives an information about the protein binding of the drug.

ii. In some cases, Vd>>> body mass. So, a very small Cp^0 will result in, as the drug will be concentrated in tissues and organs. (Shargel, Andrew, & Wu-Pong, 2005)

iii. When Vd is large: the drug is found abundantly concentrated in extravascular tissues.

iv. When Vd is 100%, there is the concentration of drug only in specific tissues, e.g. ***digoxin.***

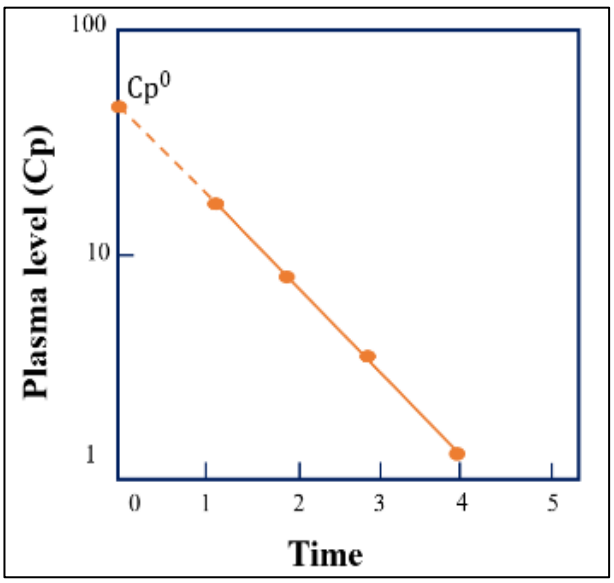

Figure 4: Semi log graph giving the value of Cp

Clearance

Clearance is defined as *"A measure of drug elimination from the body without identifying the mechanism or process."*

- Denoted by *Cl*
- Unit: mg/hr, ml/hr
- It assumes the whole body as one compartment that eliminates the drug.
- The purpose of calculating clearance is to determine what amount of plasma has been cleared of the drug per unit time.
- It can be expressed in terms of the fraction.
- Clearance may be expressed as elimination of

Amount per Unit Time

Units of mg/min and mg/h are used. This is more convenient in the case of zero-order kinetics.

Volume per Unit Time

- Glomerular filtration in body is 120ml/min.
- Useful in first-order kinetics.
- Elimination is dependent on Cp.
- Rate of change of drug explained by formula: $dC/dt = kC$
- *If Cp>>>, drug removal rate>>>.*
- Constant for a first-order process

$$\frac{\frac{dDB}{dt}}{Cp} = -kVD = -Cl$$

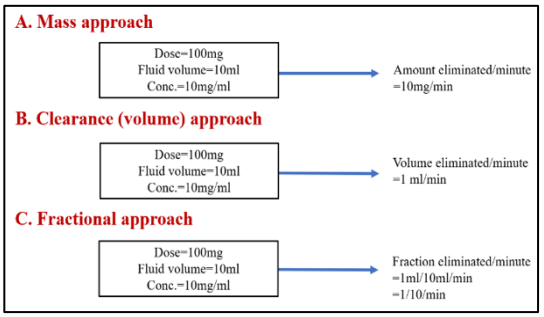

Figure 5: Diagram Illustrating three different ways of Describing Drug Elimination after a dose of 100 mg Injected IV into a volume of 10 mL

Clearance from Drug-Eliminating Tissues

Where,

CLT is the total clearance, Clr is renal clearance, and ClNR is non-renal clearance primarily via hepatic route.

Clt=Clr+Clnr

The fraction of drug excreted unchanged in urine 'Fe' and fraction excreted after metabolism 'Fm' may also be calculate by following formulas:

$$Fe = \frac{Ke}{KE},$$

$$Fm = \frac{Km}{KE}$$

(Skip, Bednarska, & Laskowski, 2014)

Intravenous Infusion

Every drug can be given IV either at once (bolus) or via infusion at a continuous rate slowly, a specified amount entering the body at a time instead of all at once. The method used depends on the drug, whether it should be given in the form of a bolus or infusion.

For example, phenytoin must always be given via infusion, with a maximum infusion rate of 0.05g/min (to avoid toxicity) at a slow pace. These drugs follow zero-order kinetics when given via infusion. Cp can be monitored in this case.

In the case of IV infusion, as initially the amount of drug in the body is zero, and with the increasing time, only a specified amount of drug enters the body according to the fixed infusion rate, so the rate of change of drug entering the body would be negligible, it is considered to be equivalent to zero, as shown in the following formula:

$$\boldsymbol{dCp/dt = 0}$$

When the level of the drug becomes constant in the body, showing a linear graph, a steady-state concentration (CSS) has been achieved, as the rate of absorption is now equal to the rate of elimination (Tang, Xiao, & Pharmacodynamics, 2007).

So, steady-state concentration is shown as:

Rate of Drug Absorbed (Input) = Rate of Drug Eliminated (Output)

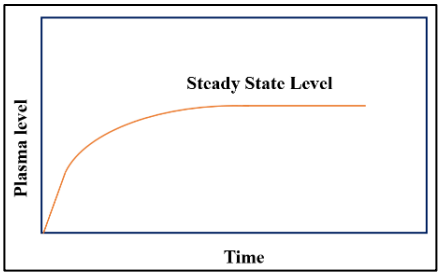

Figure 6: Graphical representation Plasma Level of drug vs time

One-Compartment IV Infusion

When a drug is administered via IV infusion, the absorption will be azero-order process, as the rate is independent of the initial concentration; however, the elimination process would be afirst-order process, it will be dependent on the initial concentration (WU, 2000).

Infusion rate *R* is a very important factor in IV infusion, as it controls the amount of drug entering the body at a given time interval. So, the the rate of change of drug in the body in case of IV infusion can be provided by the following equation:

$$\frac{dDb}{dt} = R - kDb$$

'k' will follow afirst-order kinetics as it has to do with elimination, while 'R' will follow zero-order kinetics as it has to do with absorption.

Estimation of Pharmacokinetic Parameters

Elimination phase of a drug is adequately studied by prediction of the following pharmacokinetic (PK) models that outline the whole elimination procedure and help develop optimum dosage regimens for required clinical efficacy. Following are the PK parameters calculated:

i. The elimination rate constant (k)
ii. Elimination half-life (t1/2)
iii. Drug clearance (Cl)

Elimination Rate Constant (k)

Experimentally after a drug has been administered in the form of IV infusion, the plasma levels are monitored at time intervals and are plotted on a graph. This graph shows that initially, the concentration is zero, which gradually rises, which indicates an increase in absorption rate, then a point is reached where the rate of absorption is equal to the rate of elimination, indicating the steady-state concentration indicated by point *A*.

The slope before point A shows zero-order kinetics of absorption, while the slope after point A shows the first-order kinetics of elimination of the drug in the body.

Slope: -k/2.3

Elimination Half-Life

The Cp vs. t graph plotted to calculate the pharmacokinetic parameters, the slope of this graph is used to calculate the value of constant k, putting it in the formula below, the unknown factor (R, or Vd, or Cp) can be found out. The following mathematical formula is generally used in this regard:

$$Cp = \frac{R}{V_D k}(1 - e^{-kt})$$

Cp=amount of drug in plasma
t=time at which Cp is calculated
Css=steady state concentration

Loading Dose Plus Infusion – One Compartment Model

Following formulas are of use when calculating the loading dose in IV infusion, loading dose is denoted by DL, and it is the first dose that is administered into the body, after that a maintaining dose is administered to keep the Cp in the required range. These formulas are of clinical significance:

Concentration in case of IV Bolus

$$C1 = C_o e^{-kt} = \frac{D_L}{V_D} e^{-kt}$$

In the case of IV Infusion

$$C2 = \frac{R}{V_D k}(1 - e^{-kt})$$

(Yamazaki et al., 2011)

Procedure to Calculate Css

Calculate the infusion rate 'R.' Use the literature values of Css, k, Vd, Clt for this purpose. Take two plasma samples and record the time 't', known as sampling time. Mae sure to withdraw the second sample at or near to the tss; time at which steady state concentration is achieved. Draw the graph of 'Cp' vs. 't' data sets. Calculate k and t1/2 from slope. If t1/2 validates the second sample was indeed taken at the steady state concentration, then Cp is assumed to equal the Css.

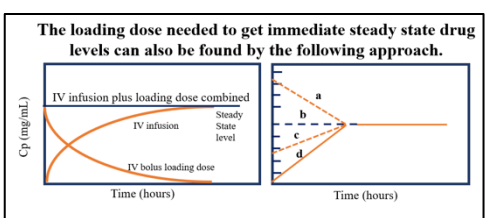

Figure 7: Graphical Representation of Loading Dose

Loading Dose Equation

Following formula can also be used to calculate the loading dose, provided that Css and Vd are known.

$$C1 = \frac{D_L}{V_d} e^{-kt}$$
$$D_L = C_{SS} V_D$$

The Volume of Distribution & Clearance

Experimentally, a drug is administered via IV infusion, and one open compartment model is used to study its pharmacokinetic and pharmacodynamic parameters. In this example, the level of drug in the body Cp is correlated to its infusion rate and clearance in the following mathematical formula; this will be of use when calculating the required infusion rate of a drug with known clearance from literature and Cp value to ensure that the drug in being administered in the right dose with a good safety profile.

$$C_P = \frac{R}{Cl}(1 - e^{-(Cl/Vd)t}$$

- It is evidently seen that the elimination rate constant k depends on the clearance and volume of distribution whereas these two terms; Vd and Cl are independent.
- Css and tss also depend on Cl and Vd.
- In case the value of Vd is constant, tss ∝1/Cl.
- This above formula states that if a drug has ↓ clearance, time required to achieve the steady state concentration plateau in the graph will ↑.
- On practical grounds, the value of Cl may be varying from one individual to another provided that the liver or kidney (organ responsible for major clearance of the drug, which may be different for different drugs) is compromised.
- Normally while clinical testing, blood samples are withdrawn an hour after the administration of IV infusion, however it may be more ideal to withdraw it after 3-4 half lives to obtain more accurate and reliable results. (Zhang, Huo, Zhou, Xie, & biomedicine, 2010)

Michaelis-Menten Elimination Kinetics

When there is sufficient evidence for the presence of nonlinearities in the PK profile of the drug understudy, the Michael-Menten elimination kinetics should be made of use (Tang, Xiao, & Pharmacodynamics, 2007). The application of PK models suggest that concentration of drug should always remain above the MEC but below the minimum toxic concentration to provide with required clinical outcomes.

However, in case of nonlinearities the equations discussed above cannot be used. For this purpose, this kinetics devises the following formulas to be used:

$$\frac{dC(t)}{dt} = -\frac{VmaxC(t)}{Km + C(t)}$$
$$C(t+0) = C0 = \frac{D}{V1}$$

Importance of Urinary Excretion Data in the Study

If the Cp-t data is not available, then the urinary excretion data can still be used to calculate the PK parameters after the administration of drug. (Brahmankar & Jaiswal, 2005)

a. Method is useful in absence of precise analytical techniques.
b. Noninvasive method.
c. Collection of samples is convenient compared to withdrawing of blood.
d. All the PK parameters can be calculated by this method.
e. Direct measurement of absolute and relative bioavailability.

Conclusion

One-compartment model, IV bolus drug injection, provides the simplest approach for estimating Vd and k. If

Vd, k, and the drug dose are known, the model equation allows drug concentration in the compartment at any time to be calculated. The volume of plasma fluid and extra-cellular fluid may be relatively constant under normal conditions. However, these volumes added together do not usually exceed numerically equal to the (apparent) Vd of the drug, which may be larger or smaller depending on how widely the drug distributes into tissues. Although the one-compartment model has limitations, it cannot be considered to provide clinically reliable outcomes. Secondly, it can only be applied to drugs that distribute rapidly through the body.

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