

A single compartment simulation model of pharmacokinetics

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ABSTRACT

For better understanding about derivation of various parameters related to pharmacokinetics, this model is developed. Animals or human volunteers are not used in this model but the principles used in pharmacokinetic studies in volunteers are incorporated. There is detailed description about setting of the model and derivation of various parameters step by step. An example is followed to illustrate the calculations involved. Possibilities of further extension of model to derive additional parameters and variations are discussed. The experience indicates that the model serves as a good demonstration to undergraduate students and a meaningful experiment for PG-students for learning and as a practical-examination exercise. The purpose of the article is to widen the use of this simple teaching tool at various centers.

Keywords: Elimination kinetics, Plasma half-life, Pharmacokinetics, Simulation model, Single compartment

INTRODUCTION

Pharmacology has been always recognized as an essential foundation for clinical sciences. It is taught to undergraduate students in their second year of medical curriculum through lectures, practical-sessions, demonstrations, tutorials and various other modalities. Pharmacokinetics (PK), an important aspect of pharmacology needs to be emphasized from the point of view of concepts to be applied during patient care in clinical practice. PK of a drug in the body is a complex process, governed by variety of factors, such as properties of drug molecule, circulation, permeability of various

biological membranes, tissue composition and affinity of tissue for the administered drug. The students need to have clear understandings about the various terminologies like volume of distribution, plasma clearance, plasma half life, elimination constant, elimination rate etc. used in the field of pk and also their clinical implications. There has to be an understanding about actual derivation of these parameters. This model is developed from this point of view.

It is known that pk studies are carried out in volunteers or in patients. The students may not have opportunity to see such an actual practice. The principles used in these studies

are incorporated in this model; it is to emphasize that; animals or human volunteers are not used in this exercise.

To conduct the pk studies in clinical practice, a dose of the drug is administered to human volunteers (of course after following the meticulous planning and observing standard guidelines). The blood samples are collected at certain interval and drug concentration in each sample is determined. A time-course of blood/plasma-drug-concentration curve is obtained, and this curve is further analyzed for calculating pk parameters.¹ Following are the steps, described briefly.

- Volume of distribution (Vd) is obtained from the ratio of dose (D) and initial concentration (C₀) after intravenous injection.¹
- From the ratio of the dose (D) given and area under curve (AUC), value of plasma clearance (CL) of the drug is obtained.¹
- Ratio of clearance (CL) and volume of distribution (Vd) gives elimination constant (k).¹
- From k one derives plasma half life (t_{1/2}).¹

In this model similar operative steps are used to develop the basic understandings regarding deriving various parameters related to pharmacokinetics.



Figure 1: Assembly for single compartment simulation model of pharmacokinetics.

Procedure involved in the model

Principals

A cylindrical transparent/semi transparent plastic vessel of volume of about 500ml to 1liter is used. A side tube is fitted at the upper level in the vessel (as shown in the figure). When the vessel is filled with the fluid, the fluid

above this side tube will over-flow. An arrangement is used to continuously stir the fluid in the vessel. An infusion set is used to continuously add water in the vessel; rate of addition of water can be controlled by the Murphy's drip. Figure 1 illustrates the instrument-arrangement.

A known quantity (150mg) of potassium permanganate (KMnO₄) is added to vessel, which is filled up with water up to the side tube (any other coloured compound like methylene blue can also be used). As stirring continues throughout there will be mixing of KMnO₄ crystals and a uniform concentration of KMnO₄ will be produced in the vessel. A sample of a few milliliters of fluid is collected from the vessel and is submitted for the estimation of KMnO₄ concentration using calorimetric method. Thus, an initial concentration (C₀) of KMnO₄ in the vessel is obtained. Quantity of KMnO₄ added initially (say 150mg) represents dose (D). A ratio of D/C₀ gives volume to which KMnO₄ is distributed (Vd). This should be equal to the fluid in the vessel after filling it up to the side tube; which can be physically confirmed.

After obtaining these two parameters (D and Vd) further procedure is followed. From the infusion set water is added at a particular rate into the vessel containing KMnO₄ solution. As stirring is continuously kept on, there will be uniform mixing of the water which is being added. Because of addition of water there will be overflow from the side tube; the Vd will not change. As result of addition of water the KMnO₄ solution in the vessel will get diluted as time passes. Samples of fluid are collected at regular interval (say 5min) till fluid is diluted to a great extent. Each sample thus collected is subjected to estimation of KMnO₄ concentration and a time course of concentration is obtained based on these values.

From the curve an AUC is derived by square counting method.² Ratio of D/AUC will give the value of CL.¹ Further k and t_{1/2} will be calculated. The steps are further illustrated by actual calculation of the data obtained by experimenting with the model.

An alternative method of deriving t_{1/2} from log concentration time curve is illustrated with the help of the actual data generated using the model.³

Illustration with an example

- Dose: Potassium permanganate added: 150mg
- Initial concentration: 230µg per ml

Dose / Initial concentration = Vd (Volume of Distribution)..... (Equation 1)

Calculated Volume of distribution (Vd): 652ml

(This calculated value is not much different than the actual value of 660ml, the volume of the vessel used in model).

Based on the data generated using the model a curve of concentration in the vessel vs time was plotted as shown in the Figure 2.

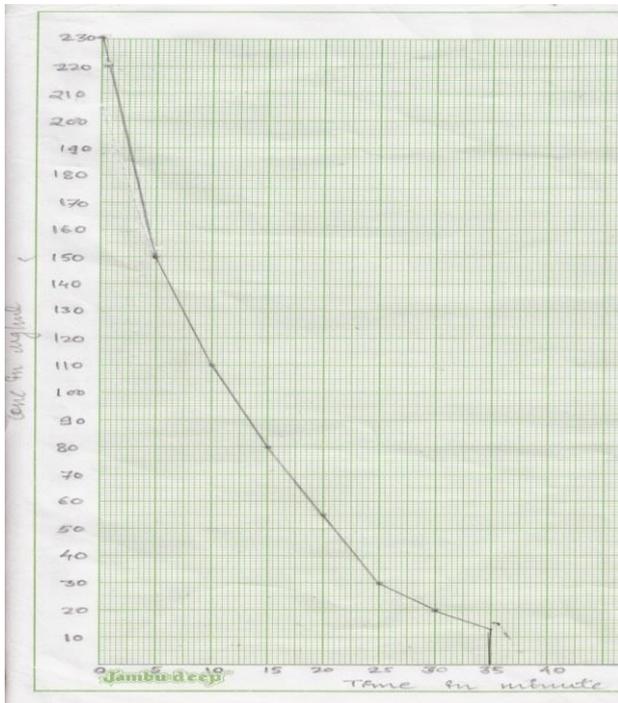


Figure 2: Graphic presentation of concentration in vessel vs time.

Area Under curve (AUC) calculated based on the curve: 2775µg/ml*min.

Clearance is obtained using formula:

$$CL = \text{Dose} / \text{AUC} \dots \text{(Equation 2)}$$

$$\text{Clearance (CL)} = 150,000\mu\text{g} / 2775\mu\text{g/ml}\cdot\text{min} = 54.05\text{ml/min}$$

Elimination constant is derived based on the formula:

$$\text{Elimination constant (k)} = CL / V_d \dots \text{(Equation 3)}$$

$$k = 54.05\text{ml/min} / 652 \text{ ml} = 0.08 \text{ per min}$$

Within how much time concentration will be half the original concentration?

This is derived using the formula:

$$C_t = C_0 * e^{-kt} \dots \text{(Equation 4)}$$

In the above equation If $C_t = \frac{1}{2} C_0$, one gets the following equation for $t_{1/2}$

$$t_{1/2} = \ln 2/k \dots \text{(Equation 5)}$$

$$t_{1/2} = 0.693/0.08 \text{ (where value of } \ln 2 \text{ is } 0.693) = 8.35\text{min}$$

Thus, in the present model half life of disappearance of potassium permanganate calculated is 8.35 min. This is dependent on rate of administration of clear water from the infusion set.

Another method to derive $t_{1/2}$ using a graphic method is illustrated below:

Instead of concentration vs time curve, log concentration vs time curve is plotted as shown in Figure 3.

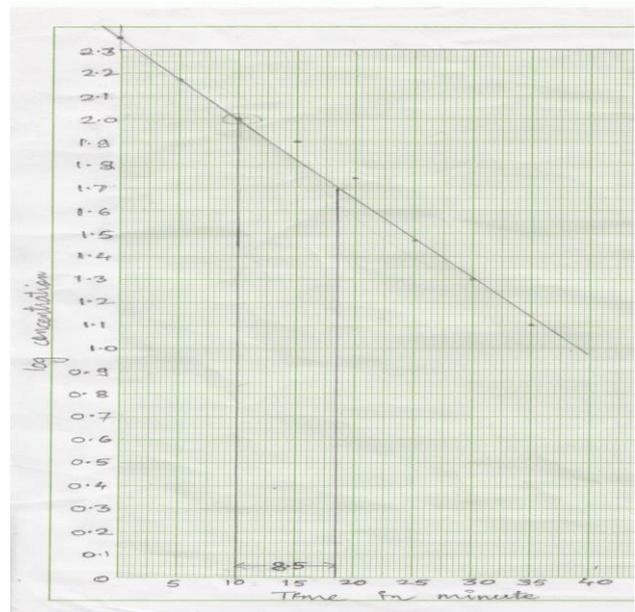


Figure 3: Graphic presentation of log concentration vs time.

At a particular time, the concentration on this log-concentration–time curve is noted. Say, at 10min concentration noted was 100µg/ml (log value 2.00). Now, time at which the concentration happens to be half of earlier value (50µg/ml; log value 1.7) is noted on the graph (which is 8.5 min in the Figure 3). A difference of time for both the concentrations gives $t^{1/2}$. Thus, it took 8.5min to reach half of the earlier concentration.

Any value can be taken on the graph and this kind of calculation can be done to know the $t_{1/2}$.

DISCUSSION

Different compartment and non-compartment pk models are used to calculate plasma concentration of the drug.^{4,5} These models are based on normal population pharmacokinetic data sets. Ours is single compartment simulation model of pharmacokinetics; illustrates derivation of various parameters in simplified way. Potassium permanganate is used here as a material which represents “drug” it can be replaced by any suitable substance, concentration of which can be assessed by simple method.

With the use of this model the students are expected to get the clear idea of term 'volume of distribution'. There can be discussion regarding the volume of distribution of various drugs in the various compartment of the body. Importance of 'volume of distribution' along with the distribution in various compartments with suitable examples can be emphasized for the benefit of students.

Concept of 'plasma clearance' and its relationship with 'plasma $t_{1/2}$ ' can be well illustrated using the model. Various factors controlling the CL and $t_{1/2}$ can be discussed; examples of various clinically useful drugs can be emphasized to impress upon the importance of the concept.

It is obvious that the rate of addition of water from infusion set will determine the value of clearance in the present model. If rate is faster clearance will be more; and vice versa. This represents body's drug-metabolizing and eliminating system.

With certain modifications and extensions of the procedures additional aspects of pharmacokinetics can be illustrated. Following are such considerations:

Multi-compartmental model

Though the present model represents a single compartment model, a multi-compartment can be developed by inserting an adsorbent material which can adsorb the substance representing "drug". Additional vessels with membrane inserted in the main vessel may be an alternate way to create a separate compartment.

Steady state concentration

Concept of steady state concentration and practical aspects related to this can be illustrated by making following extension of the experiment. Now imagine the vessel is filled with water, no potassium permanganate is added; now at a certain rate (with which value of clearance is established in earlier experiment) water is added from the infusion set. This will set the system having certain potential of clearance and $t_{1/2}$. To this system, from a separate infusion set, a solution of known concentration of potassium permanganate is infused at certain rate. It is expected that the concentration of potassium permanganate will gradually increase in the fluid in the vessel. At certain time the potassium permanganate-concentration in the vessel will reach a steady state. One can calculate the time required to achieve the steady state of concentration and establish any relation of this time to that with $t_{1/2}$ of the system (set by a certain flow rate of clear water from the infusion set).

One can determine the level of steady-state-concentration achieved and further establish any relation of the level of steady-state-concentration to the rate of drug administration, Vd, CL and $t_{1/2}$, if any. Concept of setting a rate of drug administration to achieve a desired steady-

state- concentration in the light of CL and $t_{1/2}$ can be made simple with use of this model.

These aspects can be demonstrated to the UG students. For PG students these exercises can be a part of training during PG studies and PG examination in Pharmacology.

Zero order kinetics of elimination

Analysis of AUC and estimation CL, $t_{1/2}$ in the model described above represents first order of kinetics of elimination. With following modification in the experimental protocol the concept of zero order of kinetics of elimination can be illustrated.

The vessel is filled up to the level of side tube. A known quantity of potassium permanganate is added. Initial concentration of potassium permanganate in the vessel fluid is estimated. Vd is determined. Now, do not allow any of flow of water from the infusion set. To this system, from a separate infusion set, infuse a dilute solution of known concentration of sodium bisulfate / sodium metabisulfite at certain rate.

Sodium meta- bi-sulfite decolorizes potassium permanganate solution.⁶ Serial samples of a few ml are collected at a fixed interval over the time till potassium permanganate concentration is negligible. Here too, a concentration- time course is plotted. This curve will be different than that obtained earlier. Earlier curve from where, CL and $t_{1/2}$ are determined represents the first order of kinetics of elimination; while this curve obtained experimenting with sodium meta-bi-sulfite represents the zero order of kinetics of elimination. The graphic representation of first and zero order kinetics is illustrated in Figure 4.

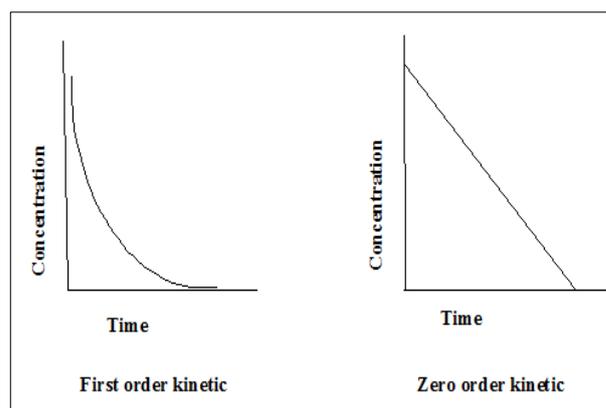


Figure 4: Graphical representation of elimination kinetics.

Concept of the first and zero order of kinetics of eliminations can be well emphasized and their clinical implications can be stressed with suitable examples. Possibility of saturation of drug metabolizing enzyme system with higher doses of the drug and conversion of

first order kinetics to zero order kinetics can be well illustrated. Sudden rise of blood concentration (and hence adverse effects) with small increment in dose is associated with this change in kinetics from first order to the zero order can be well emphasized while demonstrating the data with the model.

CONCLUSION

It is concluded that this model illustrates basic concepts of pharmacokinetics. As the model does not involve use of animals and human volunteers, it can be easily used as routine teaching tool. It can very well fit in time frame for the practical class for undergraduate students. Students will develop the clear idea about generating pharmacokinetic information with an experimental protocol. They will have opportunity to discuss the clinical importance of pk parameters in day-to-day practice of patient-care.

For PG students, it will be useful experimental model during their study to develop the skill of handling the data; they may add innovative ideas to further modify the model to illustrate more complicated issues in pharmacokinetics. Of course, the model can be a useful tool in the post graduate examination in Pharmacology.

It is to note that the model is being used as teaching tool for UG students in this department for last 5 years. It is also in used in the department of Pharmacology at Government Medical College, Surat (Gujarat, India) for UG students and as a PG-examination-exercise for more than a decade. The purpose of the article is to widen the use of this simple teaching tool at various centers.

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