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TOPICS IN CLINICAL RESEARCH

Introduction to Pharmacokinetics

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One of the most interesting and challenging aspects of early phase clinical trials is studying the pharmacokinetics of a new drug, in order to determine how a body processes it. For those readers with limited knowledge of the subject, this article is intended to provide an overview of pharmacokinetics, and the pharmacokinetic terms that are commonly used in medical journals. The article will also introduce the concepts of bioavailability, therapeutic range, accumulation and steady state, and dose proportionality.

Defining pharmacokinetics

The pharmacokinetics of a drug is particularly important during the early stages of drug development, namely in pre-clinical, phase I and phase II studies. In order to produce an effect, a drug must reach its target site at an adequate concentration. This involves several processes collectively called pharmacokinetics. Generally, the processes are: absorption, distribution, metabolism and excretion (ADME).

Table 1 ADME

Process	Description
Absorption	Before a drug can exert a pharmacological effect in tissues, it has to be taken in to the bloodstream — usually via mucous surfaces like the digestive tract (intestinal absorption). Absorption is the process that involves drug movement from the site of entry into the bloodstream.
Distribution	Distribution is the process by which a drug is transported in body fluids from the bloodstream to the tissues of the body. A drug can be administered through a variety of routes, including intramuscularly, intravenously, subcutaneously, orally, or via nasal passages, ear, eye, and more. After administration, a drug will distribute itself into all of the body's compartments and tissues that it is able to. The time it takes for this to occur is called the distribution phase, and is usually rapid. A drug is said to be distributed into a theoretical volume, called the volume of distribution (V_d). This volume is usually measured in litres, and is considered theoretical because it is based on sampling drug concentrations immediately after dosing, with the assumption that the drug is uniformly distributed throughout the body.
Metabolism	Metabolism is the process by which a drug is chemically inactivated (broken down by enzymes) so that it can be excreted from the body.
Excretion	Excretion is the process by which a drug is removed from the site of action and eliminated from the body. Immediately after a dose of drug is administered, the body begins to

Process	Description
	eliminate by hepatic metabolism, renal excretion, or both. The elimination process can sometimes follow first-order kinetics, whereby constant proportion of the drug is eliminated from the body during each unit of time. If the drug goes into several compartments and is eliminated from these compartments at different rates, then the pharmacokinetics become more complicated. This topic will be explored further in upcoming articles of SciAnNews.

Key pharmacokinetic parameters

In this article, the following pharmacokinetic parameters will be discussed:

- Maximum drug concentration (C_{max})
- Trough drug concentration (C_{trough})
- Time of maximum concentration (T_{max})
- Elimination rate constant (k_e)
- Systemic clearance (Cl)
- Half-life (T_{half})
- Area under the drug concentration versus time curve (AUC)
- Volume of distribution (V_d)

After a drug is administered, it is absorbed in the body, and will reach a peak concentration, C_{max}, at time T_{max}. Trough concentration, C_{trough}, is the minimum concentration found in a dosing interval. In the case of multiple dosing, it is obtained immediately prior to the next dose.

Elimination of drugs that follow first-order kinetics is described by an elimination rate constant, which represents the decrease in drug concentration per unit of time (e.g. hr^{-1}). This constant is mathematically related to two other important parameters, namely drug clearance (Cl), and half-life (T_{half}). Clearance is a descriptive term used to measure the rate that a drug is irreversibly removed from the body. It represents the theoretical volume of blood that is completely cleared of drug per unit time (e.g. mL/min). Clinicians may be familiar with the notion of clearance from using creatinine clearance in order to describe renal function.

Some drugs are metabolized quickly, while others can take a long time before they are eliminated. We use of term "half-life" in order to quantify this process. Half-life is the time required for the concentration of drug to decrease by 50% of the current concentration. If a drug follows first-order elimination, then it would take about 5-6 half-lives for the drug to be completely removed from the body. For example, a drug with an elimination half-life of about 4 hours should be completely eliminated from the body after 1 day of taking their last dose. If, however, a drug has an elimination half-life of about 48 hours, the drug would not be completely eliminated from the body until 10-12 days after the last dose. Thus, a patient who stops this therapy due to a side effect may find the symptom still persists several days after discontinuation of the drug. The biggest hazard of using half-life to describe drug elimination is that most drugs do not have a single half-life, but have multiple ones. The most common T_{half} used by clinicians is an overall elimination half-life that ignores different phases of elimination, and is calculated using non-compartmental modelling.

Another important pharmacokinetic term is AUC, the area under the concentration-time curve. This term can be used to calculate overall clearance values for a drug. In addition, AUC is frequently used to compare drug exposures achieved with different drug doses.

As previously discussed in this article, the volume of distribution (V_d) is used to quantitatively describe the distribution of the drug throughout the body, on the assumption that the drug is uniformly distributed throughout the body.

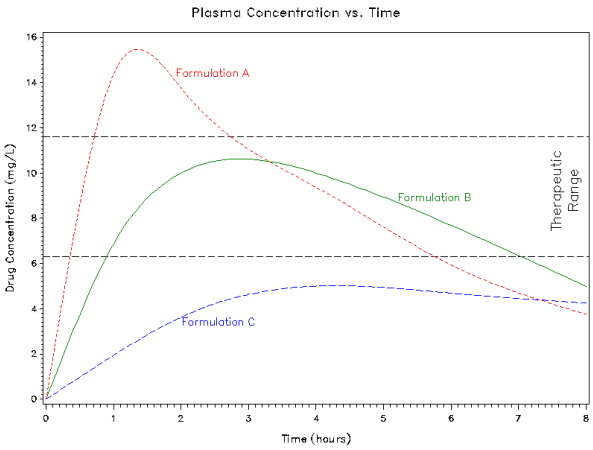
Bioavailability

Bioavailability, commonly denoted as "F", is used to describe how much drug reaches the circulation system after administration. The bioavailability of an intravenous drug dose is assumed to be 100%. In the case of oral administration, F is calculated as the ratio of drug concentrations (using AUCs) after giving the drug orally, compared with the same dose given intravenously. A drug with a bioavailability of 10%, for example, will provide 10 milligrams of active drug to the circulation system for each 100 milligrams of administered drug.

Therapeutic Range

The therapeutic range of a drug is the optimal range of drug concentration that will provide high efficacy while maintaining a low risk of dose-related toxicity.

The figure to the right illustrates the plasma concentration-time curves for three theoretical formulations of different doses and absorption rates. In this example, Formulation A would not be considered a safe choice, as it could be potentially toxic to a patient. Formulation B appears to be effective, staying within the therapeutic range from 1 to 7 hours following dose administration. The dosage for Formulation C appears ineffective, as the plasma concentration achieved with this formulation never reaches the therapeutic range.



Accumulation and steady-state

When the same dose of a drug is re-administered before the previous dose is completely removed from the body, there's an ongoing process of drug absorption and, concurrently, an ongoing process of drug removal. The resulting concentration will be higher than that achieved with the previous dose. This is referred to as drug accumulation, which is a function of the elimination rate half-life of the drug. Eventually, there comes a point when the amount of drug administered is the same as the amount of drug eliminated within a given time interval. In the figure to the right, this point in time is reached at the third day of dosing. We call this "steady state", which can take between 5 to 6 half-lives for a medication to reach. Medications with short half-lives reach steady state relatively quickly, while those with longer half-lives take more time to reach steady state.

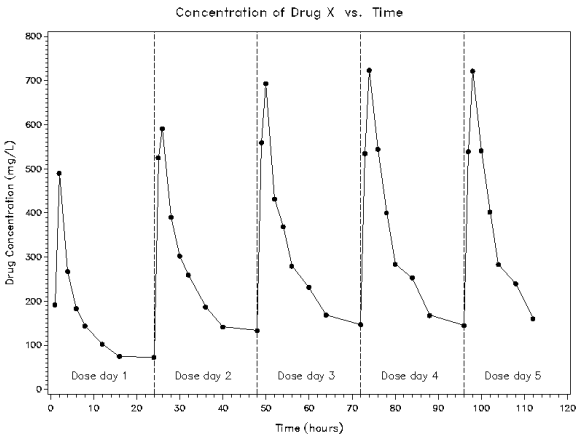


Table 2 below demonstrates the proportion of steady-state serum concentrations attained after the given number of half-lives. For example, the concentration is 94% of the way to a steady-state level after 4 half-lives. Note that this holds true regardless of dose, initial concentration, or final concentration, but **only** in the case of first-order kinetics.

Table 2 Proportion of Steady State Concentrations

Number of half-lives	% of steady-state reached
½	29.3
1	50.0
2	75.0
3	87.5
4	93.7
5	96.9
6	98.4
7	99.2

Dose Proportionality

In order to provide safe and effective dosing to patients, knowing how a drug works at different dose levels is essential. However, obtaining a complete pharmacokinetic profile for all possible doses of a drug is practically impossible. If a drug possesses the property of dose proportionality, then predicting pharmacokinetic effects in different dose ranges is easily done. This property, also known as dose linearity, implies that the rates of absorption, distribution, metabolism, and elimination remain constant over the dose range, and that the AUC and maximum concentrations increase in direct proportion to the dose.

Consider the three drug concentration vs. time profiles illustrated to the right. Intravenous doses of 10 mg, 20 mg, and 40 mg of the same drug compound were given to patients. The calculated pharmacokinetic parameters are shown in Table 3.

The drug is shown to exhibit attributes of dose proportionality in the calculations of AUC and Cmax. We also observe that the elimination rate constant (calculated by using the log concentration vs. time curve), as well as the half-lives and clearances are the same.

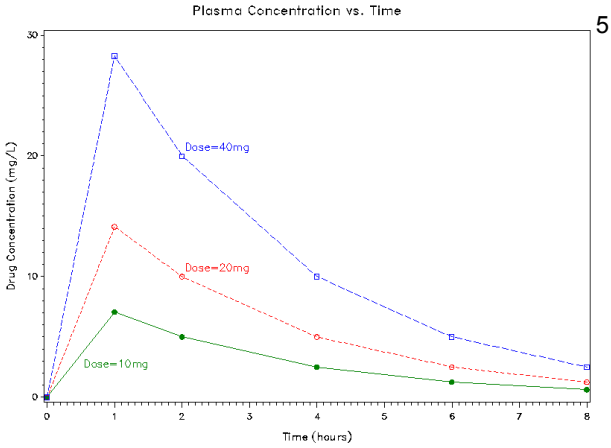


Table 3.

Parameter	10 mg dose	20 mg dose	40 mg dose
First-order elimination rate constant (1/hr)	0.347	0.347	0.347
Half-life (hr)	2.0	2.0	2.0
T_{max} (hr)	1	1	1
C_{max} (mg/L)	7.07	14.14	28.29
AUC (hr*mg/L)	22.70	45.40	90.80
Volume of distribution (L)	1.18	1.18	1.18
Clearance (L/hr)	0.408	0.408	0.408

Conclusion

Although pharmacokinetics is largely a mathematical science, the concepts described in this article should be known to those who provide care to patients taking medication, or those who read scientific articles based on new drug research. The ability to interpret PK results, and to acquire insight regarding the accumulation, steady state, and dose proportionality characteristics of a drug, is essential if one wishes to gain a clear understanding of a drug's properties. This background knowledge will guide one to make intelligent decisions for modeling pharmacokinetic data. Upcoming SciAnNews articles will include introductions on modeling data using non-compartmental and compartmental methods.

References

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