Quest Journals
Journal of Research in Pharmaceutical Science
Volume 10 ~ Issue 4 (2024) pp: 39-49
ISSN(Online) : 2347-2995
www.questjournals.org

Research Paper

Study of General Pharmacokinetic and Pharmacokinetic Modelling

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ABSTRACT
Characterizing the relationship between the pharmacokinetics (PK, concentration vs. time) and pharmacodynamics (PD, effect vs. time) is an important tool in the discovery and development of new drugs in the pharmaceutical industry. The purpose of this publication is to serve as a guide for drug discovery scientists toward optimal design and conduct of PK/PD studies in the research phase. This review is a result of the collaborative efforts of DMPK scientists from various Metabolism and Pharmacokinetic (MAP) departments of the global organization Novartis Institute of Biomedical Research (NIBR). We recommend that PK/PD strategies be implemented in early research phases of drug discovery projects to enable successful transition to drug development. Effective PK/PD study design, analysis, and interpretation can help scientists elucidate the relationship between PK and PD, understand the mechanism of drug action, and identify PK properties for further improvement and optimal compound design. Additionally, PK/PD modeling can help increase the translation of in vitro compound potency to the in vivo setting, reduce the number of in vivo animal studies, and improve translation of findings from preclinical species into the clinical setting. This review focuses on three important elements of successful PK/PD studies, namely partnership among key scientists involved in the study execution; parameters that influence study designs; and data analysis and interpretation. Specific examples and case studies are highlighted to help demonstrate key points for consideration. The intent is to provide a broad PK/PD foundation for colleagues in the pharmaceutical industry and serve as a tool to promote appropriate discussions on early research project teams with key scientists involved in PK/PD studies.

***R**eceived 11 Apr., 2024; **R**evised 21 Apr., 2024; **A**ccepted 23 Apr., 2024 © The author(s) 2024.*
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I. INTRODUCTION

Pharmacokinetics is the study of how drugs move through the body. It involves understanding the absorption, distribution, metabolism, and excretion (ADME) of drugs, which collectively determine the drug's concentration in the body over time. [69]Absorption refers to the process by which a drug enters the bloodstream from its site of administration, such as the digestive tract or muscle tissue. Distribution involves the movement of the drug from the bloodstream to various tissues and organs in the body. Metabolism, or biotransformation, is the process by which the body chemically changes a drug into a metabolite that is easier to excrete. Excretion is the elimination of the drug or its metabolites from the body, usually through the kidneys or liver. [43]Pharmacokinetic principles are essential for determining the appropriate dosing regimen for a drug, understanding drug interactions, and predicting how changes in physiology (such as liver or kidney disease) may affect drug levels in the body. [1]

Effective and successful pharmacokinetics/pharmacodynamics (PK/PD) studies during drug discovery and development phases require input from scientific experts in complementary disciplines in the pharmaceutical industry. In the majority of cases, the pharmacodynamic portion of PK/PD studies (e. g. , animal dosing and measurement of response) are conducted by pharmacology laboratories within a given disease area whereas the measurement of concentrations and evaluation of pharmacokinetics are conducted by DMPK laboratories. In some cases pharmacokinetics are not determined in the same animals used in the PD study. Rather, the PK and PD datasets might be generated completely independent of each other, not only in different laboratories but also different timeframes. In the latter scenario, generation and reporting of data can happen in isolation, and project teams are then faced with downstream integration and evaluation of results that lack an

integrated analysis defining a concentration and effect relationship. Optimally, when PK/PD studies are designed and conducted, the PK/PD analysis, conclusions and interpretations are performed by both DMPK and pharmacology experts, with input from other relevant partners (e. g. , formulation and mathematical modeling experts). The resulting report thus reflects integration of all relevant data and addresses the hypothesis or question asked at the outset of the study. The report will capture any assumptions made in the analysis and suggest what subsequent studies the results enable, and reflects shared ownership and responsibility of both the DMPK and pharmacology experts. The major objective of early drug development is to select promising compounds and to identify potentially safe and effective doses and dosing regimens. Integration of PK/PD in early development helps with compound selection and guides creation of an efficient clinical development strategy.

II. KEYWORDS

General Study Of Pharmacokinetics, Clinical Study, Essential Models, Analysis, Abbreviation, Conclusion, Reference.

III. LITERATURE OF REVIEW

• **"Pharmacokinetics in Drug Development: Advances and Applications"** by Peter L. Bonate. This book provides a comprehensive overview of pharmacokinetic principles and their application in drug development, covering topics such as bioavailability, clearance, and drug interactions. [Professional Literature]

• **"Pharmacokinetics and Pharmacodynamics of Abused Drugs"** edited by Steven B. Karch. This book reviews the pharmacokinetic and pharmacodynamic properties of commonly abused drugs, including opioids, stimulants, and sedatives, and their implications for drug abuse and addiction.

• **"Clinical Pharmacokinetics: Concepts and Applications"** by Malcolm Rowland and Thomas N. Tozer. This textbook covers the fundamental concepts of pharmacokinetics and their application in clinical practice, including drug dosing, therapeutic drug monitoring, and pharmacokinetic modeling.

IV. GENERAL STUDY OF PHARMACOKINETICS

Determining the delivery, exposure and disposition of a therapeutic agent in nonclinical species is a critical consideration in any early drug development program to enable success in the clinic. Understanding these key pharmacokinetic elements are essentially captured in the classical areas of Absorption, Distribution, Metabolism and Excretion (ADME). It is not uncommon for Sponsors to attempt to solely rely on toxicokinetic (TK) data to describe the relationship between dose and exposure for all dose levels. However, this is not the goal of the toxicokinetic analysis which is intended to demonstrate adequate exposure in animal toxicology species, in order to determine toxicity and any dose-dependency thereof. There are some important differences between the ADME information that can be determined at high dose levels intended to assess the safety and toxicity of a product, i. e. , the Toxicokinetics as compared to that determined in the pharmacologically / therapeutically active dose range i. e. , the Pharmacokinetics (PK). Toxicology dose levels are often too high to fully define the PK of the drug, especially in the dose range relevant to pharmacodynamic effect or clinical efficacy. Dedicated pharmacokinetic studies in parallel to or as part of the pre-clinical pharmacodynamic studies are a pivotal part of understanding the potential effectiveness of a molecule and defining the anticipated pharmacologically active clinical dose level and target exposure. [5]

04. 01. ABSORPTION

Saturation of absorption may distinctly prolong drug delivery, lowering peak exposure (Cmax), which is often the key parameter tied to pharmacodynamics. Depending on clearance from the delivery site before being absorbed (e. g. passing through the gut), either the same AUC or a diminished total exposure might be achieved. [13]

04. 02. DISTRIBUTION

The shape of the exposure-time curve can be substantially altered at higher dose levels if the high circulating drug concentrations provide a driving force for distribution to tissues not accessed by the lower pharmacologically active drug levels. The re-circulation of drug to plasma from these compartments can significantly extend the plasma half-life of a drug well beyond that achieved at pharmacologically active dose levels. [24]

04. 03. METABOLISM

Saturation of metabolic processes at high doses would clearly produce prolonged exposure and potentially indicate a much higher steady state exposure than would be achieved at pharmacologically active dose levels. On the other hand, induction of metabolic processes by higher doses could result in more rapid clearance. [10]

04. 04. EXCRETION

Saturation of excretion mechanisms at higher doses would impact the steady state exposure in a similar fashion to saturated metabolism. Induction of an alternate excretion pathway due to excess drug at higher dose levels could substantially impact the entire exposure-time profile. [13]

V. CLINICAL STUDY

05. 01. UNDERSTANDING EXPOSURE PARAMETERS IN THE PHARMACOLOGICALLY-ACTIVE DOSE RANGE

As indicated above, different aspects of the exposure-time profile for a drug are critical to different outcomes. Beneficial and adverse effects can be either dose-dependent or activated once exposure passes a threshold level depending on the target and mechanism of action. Some effects wane with continued activation of the target, while others continue to increase in severity with continued target engagement. As such, while both pharmacodynamics and toxicity can be impacted by peak exposure (Cmax) and total exposure (AUC), it is important to also understand the other pharmacokinetic parameters in order to determine the potential effectiveness and optimal dosing regimen for a novel therapeutic. A vital part of defining the dosing regime, achieving suitable available drug for target engagement, and achieving beneficial pharmacodynamic activity is the achievement of steady state drug levels. [47]This is defined as the dosing conditions wherein exposure is reproducible following each subsequent new dose administration (where the amount in is equal to the amount out). However, the achievement of steady state and the exposure parameters at each dose level are greatly impacted by the ADME factors described above and must be defined in the dose range relevant to clinical use, not just the toxicologically active dose range.

05. 02. USING PRE-CLINICAL PHARMACOKINETICS IN CLINICAL STUDY PLANNING

The primary goal of the pre-clinical program is to support the estimation of a safe and effective dose range for testing in clinical studies. The toxicology studies provide definition of the No Adverse Effect Level (the highest dose that does not produce adverse effects) in the most sensitive nonclinical species. [54]This dose level is then converted to a Human Equivalent Dose (HED) on a comparative body-surface area basis, in the absence of either broader clinical pharmacokinetic data or a specific mechanistic or pharmacokinetic justification for an alternate conversion factor. Utilizing a 10x or 100x safety factor, the Maximum Safe Starting Dose is defined for the First-in-Human (FIH) study of safety and pharmacokinetics (the Phase 1 healthy volunteer study). Meanwhile, the understanding of what dose level and exposure profile will be beneficial in patients requires a more sophisticated algorithm built around understanding the following:

- The efficacious dose level in pre-clinical pharmacodynamic models.
- The related exposure and pharmacokinetics in the pre-clinical species in this dose range.
- The necessary elements to convert these dose and exposure parameters to humans.

Defining the effective dose range in an in vivo pre-clinical model of the disease is a standard component of candidate selection for most organizations. While the suitability of, and various forms of validity for, these models isn't within the scope of this article, understanding of the exposure and pharmacokinetics of the drug in these models at doses that produce clinically relevant pharmacodynamic outcomes is also critical. This pharmacokinetic profile is somewhat unique to the dose range tested in the test species (and occasionally the strain of animal used) and must be translated to a clinically relevant exposure measure. Firstly, the known interspecies differences related to the drug must be accommodated. Primarily, this relates to the differences in drug affinity and potency for the targets expressed by different species (target orthologs) and provides the basis for an adjustment in target drug concentrations based on the potency shift. Secondly, metabolic differences between species also need to be taken into account. These range from the more detailed differences in plasma protein binding and metabolic stability to the broader integrated pharmacokinetic considerations utilized in allometric scaling between species. The main goal of the pharmacokinetic investigation in pre-clinical studies is to define the anticipated pharmacologically active drug level in the target compartment (eg. Plasma or CSF). With this estimate, the safe starting dose and dose escalation scheme for the Phase 1 study can then be properly justified. This anticipated pharmacologically active concentration is also vital in determining the appropriate dose levels and exposure targets for safety pharmacology assessments which, unlike toxicology studies, are not required to be dosed to effect but rather to demonstrate a 10x or greater exposure margin between the target pharmacodynamic effect and the secondary pharmacologic action on the central nervous system (CNS), respiratory, or cardiovascular systems. Alongside the regulatory aspects of the early development program that are supported by pre-clinical pharmacokinetic data, a key risk assessment step for any program is to determine the potential therapeutic window. The simplest form of which is often predicated on the toxic dose divided by the efficacious dose (ideally in the same species). However, as discussed, the dose level achieving toxicity may have a very distinct exposure-time profile compared to the pharmacologically active dose level. Furthermore, the pharmacokinetic parameters responsible for the dose-limiting toxicity may be distinct from those responsible

for efficacy. For example, many gastrointestinal (GI) and CNS side-effects relate to a rapid rise in drug levels in specific compartments or tissues, while the efficacy may be related to continuous occupation of the target receptor for multiple weeks (eg. Re-uptake inhibitors for depression) or phasic activation of the target (eg. PYY or GLP-1 agonists in type 2 diabetes mellitus). As such the therapeutic window, and thus the development risks for a program, are better defined by relative exposure-time profiles for both pharmacodynamic and adverse effects than straight dose-level comparisons. [Reference 13]

VI. ESSENTIAL MODELS

Models have been developed to simplify conceptualization of the many processes that take place in the interaction between an organism and a chemical substance. Pharmacokinetic modelling may be performed either by noncompartmental or compartmental methods. Multi-compartment models provide the best approximations to reality; however, the complexity involved in adding parameters with that modelling approach means that monocompartmental models and above all two compartmental models are the most-frequently used. The model outputs for a drug can be used in industry (for example, in calculating bioequivalence when designing generic drugs) or in the clinical application of pharmacokinetic concepts. Clinical pharmacokinetics provides many performance guidelines for effective and efficient use of drugs for human-health professionals and in veterinary medicine. [21]Models generally take the form of mathematical formulas that have a corresponding graphical representation. The use of these models allows an understanding of the characteristics of a molecule, as well as how a particular drug will behave given information regarding some of its basic characteristics such as its acid dissociation constant (pKa), bioavailability and solubility, absorption capacity and distribution in the organism. A variety of analysis techniques may be used to develop models, such as nonlinear regression or curve stripping. [34]

Table :A : Example of a table for pharmacokinetic modeling:

S. NO.	PARAMETER	DESCRIPTION
1	**Drug**	**Name of the drug being studied.**
2	**Dose**	**Amount of drug administered.**
3	**Administration Route**	**Route of drug administration (e.g., oral, intravenous).**
4	**Time Points**	**Specific time points at which drug concentrations are measured.**
5	**Drug Concentrations**	**Concentrations of the drug in blood or plasma at each time point.**
6	**Pharmacokinetic Model**	**Mathematical model used to describe the drug's absorption, distribution, metabolism, and excretion (ADME) processes.**
7	**Pharmacokinetic Parameters**	**Parameters Parameters of the pharmacokinetic model, such as clearance, volume of distribution, half-life, etc.**
8	**Model Fit**	**Assessment of how well the pharmacokinetic model fits the observed data.**
9	**Conclusion**	**Summary of the pharmacokinetic behavior of the drug based on the modeling results.**

● NONCOMPARTMENTAL ANALYSIS

Noncompartmental methods estimate PK parameters directly from a table of concentration-time measurements. Noncompartmental methods are versatile in that they do not assume any specific model and generally produce accurate results acceptable for bioequivalence studies. Total drug exposure is most often estimated by area under the curve (AUC) methods, with the trapezoidal rule (numerical integration) the most common method. Due to the dependence on the length of x in the trapezoidal rule, the area estimation is highly dependent on the blood/plasma sampling schedule. That is, the closer time points are, the closer the trapezoids reflect the actual shape of the concentration-time curve. The number of time points available in order to perform a successful NCA analysis should be enough to cover the absorption, distribution and elimination phase to accurately characterize the drug. Beyond AUC exposure measures, parameters such as Cmax (maximum concentration), Tmax (time to maximum concentration), CL and Vd can also be reported using NCA methods. [32]

● COMPARTMENTAL ANALYSIS

Compartment models methods estimate the concentration-time graph by modeling it as a system of differential equations. These models are based on a consideration of an organism as a number of related compartments. Both single compartment and multi-compartment models are in use. PK compartmental models are often similar to kinetic models used in other scientific disciplines such as chemical kinetics and thermodynamics. The advantage of compartmental over noncompartmental analysis is the ability to modify parameters and to extrapolate to novel situations. The disadvantage is the difficulty in developing and validating the proper model. Although compartment models have the potential to realistically model the situation within an

organism, models inevitably make simplifying assumptions and will not be applicable in all situations. However complicated and precise a model may be, it still does not truly represent reality despite the effort involved in obtaining various distribution values for a drug. This is because the concept of distribution volume is a relative concept that is not a true reflection of reality. The choice of model therefore comes down to deciding which one offers the lowest margin of error for the drug involved. [21]

06. 01. SINGLE-COMPARTMENT MODEL

The simplest PK compartmental model is the one-compartmental PK model. This models an organism as one homogenous compartment. This monocompartmental model presupposes that blood plasma concentrations of the drug are the only information needed to determine the drug's concentration in other fluids and tissues. For example, the concentration in other areas may be approximately related by known, constant factors to the blood plasma concentration. [44]

In this one-compartment model, the most common model of elimination is first order kinetics, where the elimination of the drug is directly proportional to the drug's concentration in the organism. [36]

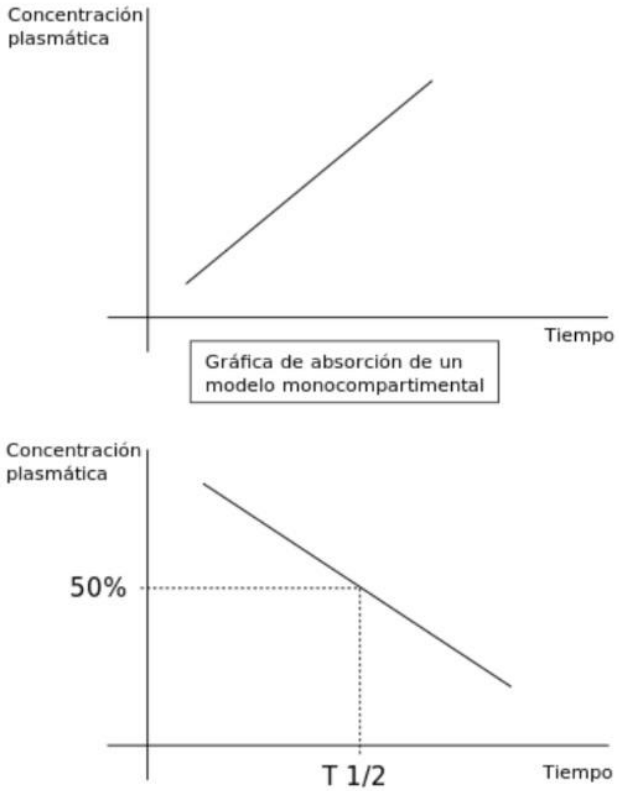

Figure : 1: Graph representing the monocompartmental action model.

06. 02. TWO-COMPARTMENT MODEL

Not all body tissues have the same blood supply, so the distribution of the drug will be slower in these tissues than in others with a better blood supply. In addition, there are some tissues (such as the brain tissue) that present a real barrier to the distribution of drugs, that can be breached with greater or lesser ease depending on the drug's characteristics. If these relative conditions for the different tissue types are considered along with the rate of elimination, the organism can be considered to be acting like two compartments: one that we can call the central compartment that has a more rapid distribution, comprising organs and systems with a well-developed blood supply; and a peripheral compartment made up of organs with a lower blood flow. Other tissues, such as the brain, can occupy a variable position depending on a drug's ability to cross the barrier that separates the organ from the blood supply. [66][67][68]

Two-compartment models vary depending on which compartment elimination occurs in. The most common situation is that elimination occurs in the central compartment as the liver and kidneys are organs with a good blood supply. However, in some situations it may be that elimination occurs in the peripheral compartment or even in both. This can mean that there are three possible variations in the two compartment model, which still do not cover all possibilities. [9]

06. 03. MULTI-COMPARTMENT MODELS

In the real world, each tissue will have its own distribution characteristics and none of them will be strictly linear. The two-compartment model may not be applicable in situations where some of the enzymes responsible for metabolizing the drug become saturated, or where an active elimination mechanism is present that is independent of the drug's plasma concentration.

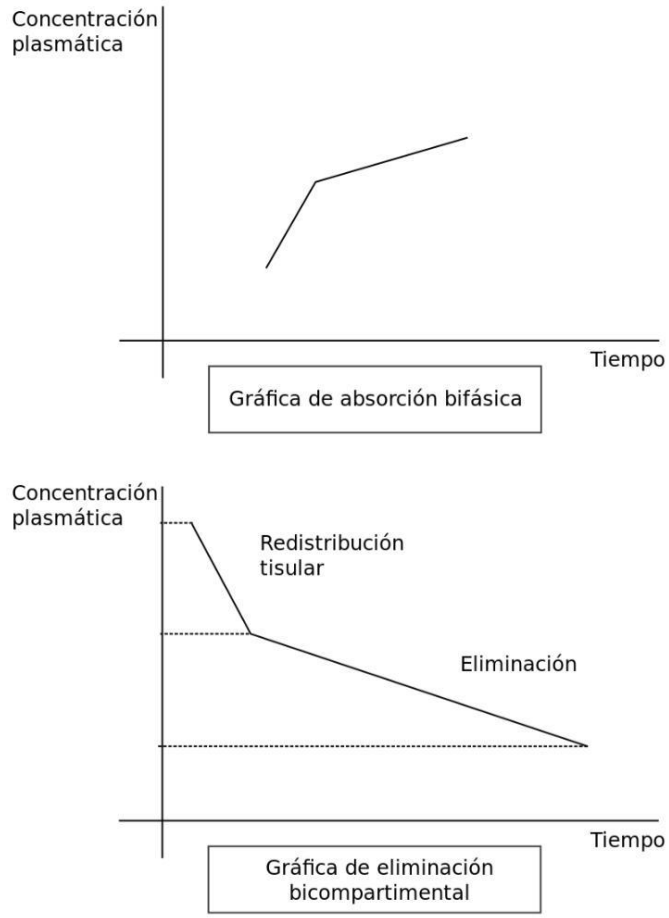

Figure :2: Graphs for absorption and elimination for a non-linear pharmacokinetic model

If we label the drug's volume of distribution within the organism VdF and its volume of distribution in a tissue VdT the former will be described by an equation that takes into account all the tissues that act in different ways, that is:

Vd_{F}=Vd_{T1}+Vd_{T2}+Vd_{T3}+…. . +Vd_{Tn}}

This represents the multi-compartment model with a number of curves that express complicated equations in order to obtain an overall curve. A number of computer programs have been developed to plot these equations. [9] The most complex PK models (called PBPK models) rely on the use of physiological information to ease development and validation.

The graph for the non-linear relationship between the various factors is represented by a curve; the relationships between the factors can then be found by calculating the dimensions of different areas under the curve. The models used in non-linear pharmacokinetics are largely based on Michaelis–Menten kinetics. A reaction's factors of non-linearity include the following:

Multiphasic absorption: Drugs injected intravenously are removed from the plasma through two primary mechanisms: (1) Distribution to body tissues and (2) metabolism + excretion of the drugs. The resulting decrease of the drug's plasma concentration follows a biphasic pattern (see figure).

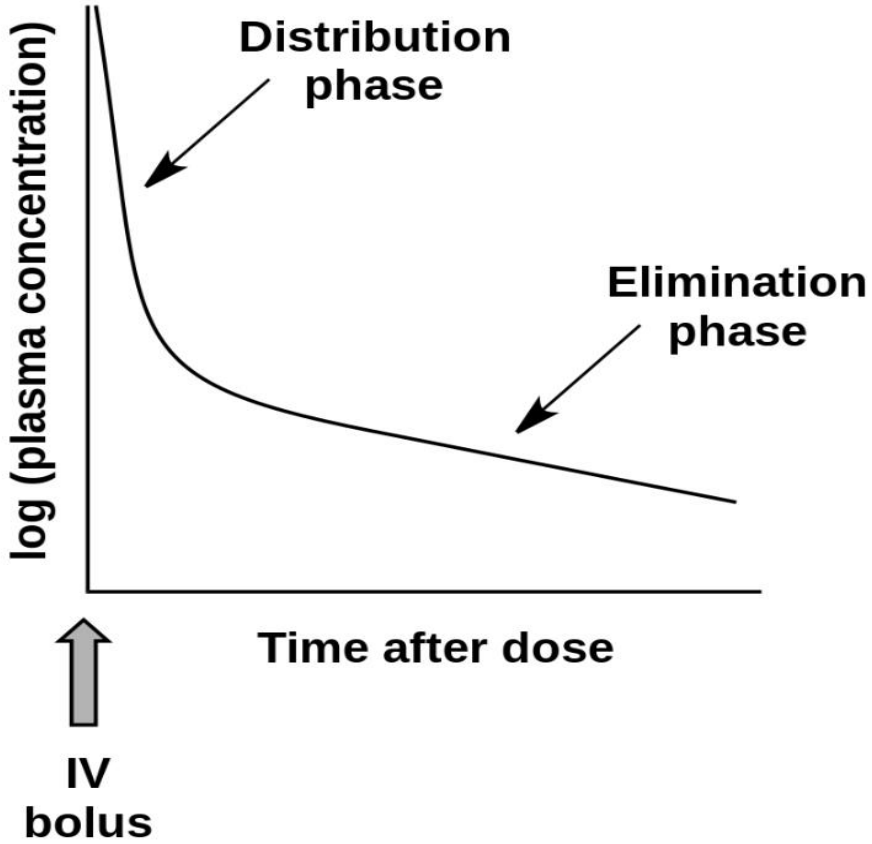

Figure :3 : Plasma drug concentration vs time after an IV dose

- ***Alpha phase:*** An initial phase of rapid decrease in plasma concentration. The decrease is primarily attributed to drug distribution from the central compartment (circulation) into the peripheral compartments (body tissues). This phase ends when a pseudo-equilibrium of drug concentration is established between the central and peripheral compartments.
- ***Beta phase:*** A phase of gradual decrease in plasma concentration after the alpha phase. The decrease is primarily attributed to drug elimination, that is, metabolism and excretion. [10]Additional phases (gamma, delta, etc.) are sometimes seen. [11]A drug's characteristics make a clear distinction between tissues with high and low blood flow.
- ***Enzymatic saturation:*** When the dose of a drug whose elimination depends on biotransformation is increased above a certain threshold the enzymes responsible for its metabolism become saturated. The drug's plasma concentration will then increase disproportionately and its elimination will no longer be constant.
- ***Induction or enzymatic inhibition:*** Some drugs have the capacity to inhibit or stimulate their own metabolism, in negative or positive feedback reactions. As occurs with fluvoxamine, fluoxetine and phenytoin. As larger doses of these pharmaceuticals are administered the plasma concentrations of the unmetabolized drug increases and the elimination half-life increases. It is therefore necessary to adjust the dose or other treatment parameters when a high dosage is required.

The kidneys can also establish active elimination mechanisms for some drugs, independent of plasma concentrations.

VII. ANALYSIS

- **Bioanalytical methods**

Bioanalytical methods are necessary to construct a concentration-time profile. Chemical techniques are employed to measure the concentration of drugs in biological matrix, most often plasma. Proper bioanalytical methods should be selective and sensitive. For example, microscale thermophoresis can be used to quantify how the biological matrix/liquid affects the affinity of a drug to its target. [13][14]

- **Mass spectrometry**

Pharmacokinetics is often studied using mass spectrometry because of the complex nature of the matrix (often plasma or urine) and the need for high sensitivity to observe concentrations after a low dose and a long time

period. The most common instrumentation used in this application is LC-MS with a triple quadrupole mass spectrometer. Tandem mass spectrometry is usually employed for added specificity. Standard curves and internal standards are used for quantitation of usually a single pharmaceutical in the samples. The samples represent different time points as a pharmaceutical is administered and then metabolized or cleared from the body. Blank samples taken before administration are important in determining background and ensuring data integrity with such complex sample matrices. Much attention is paid to the linearity of the standard curve; however it is common to use curve fitting with more complex functions such as quadratics since the response of most mass spectrometers is not linear across large concentration ranges. [15][16][17]

There is currently considerable interest in the use of very high sensitivity mass spectrometry for microdosing studies, which are seen as a promising alternative to animal experimentation. [18] Recent studies show that Secondary electrospray ionization (SESI-MS) can be used in drug monitoring, presenting the advantage of avoiding animal sacrifice. [19]

IMPORTANCE OF THE PHARMACOKINETICS :

- ✓ **Drug Development:** Pharmacology is crucial in the development of new drugs. It involves understanding the mechanisms of action, efficacy, and safety of potential medications.
- ✓ **Treatment of Diseases:** Pharmacology plays a vital role in the treatment of various diseases. Drugs are used to alleviate symptoms, cure infections, manage chronic conditions, and improve overall health.
- ✓ **Personalized Medicine:** Pharmacology is increasingly moving towards personalized medicine, where treatments are tailored to individual characteristics such as genetics, lifestyle, and environmental factors.
- ✓ **Drug Safety:** Understanding pharmacology is essential for ensuring the safe use of medications. This includes knowledge of potential side effects, drug interactions, and appropriate dosing.
- ✓ **Public Health:** Pharmacology contributes to public health by helping to control and prevent diseases through the use of vaccines, antibiotics, and other medications.
- ✓ **Education and Research:** Pharmacology is a foundational science in medical education and research. It provides the basis for understanding how drugs work and how they can be used to improve health outcomes.

VIII. ABBREVIATION

- PK (Pharmacokinetics)
- ADME (Absorption, Distribution, Metabolism, Excretion)
- Cmax (Peak Plasma Concentration)
- Tmax (Time to Reach Peak Plasma Concentration)
- AUC (Area Under the Curve)
- Cl (Clearance)
- Vd (Volume of Distribution)
- T1/2 (Half-Life)
- F (Bioavailability)
- MRT (Mean Residence Time)
- Ka (Absorption Rate Constant)
- Kel (Elimination Rate Constant)
- Tmax (Time to Peak Concentration)
- T1/2 (Half-Life)
- Css (Steady-State Concentration)

IX. CONCLUSIONS

The ICH requirements on pre-clinical pharmacokinetics are fairly open as described in M3 (R2), which states: “Further information on pharmacokinetics (PK) (e. g. , absorption, distribution, metabolism and excretion) in test species and in vitro biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects or treating for long duration (generally before phase 3). ” This might lead a Sponsor to the conclusion that toxicokinetics are sufficient to support IND-filing and Phase 1 clinical studies. However, a detailed understanding of the pharmacokinetics of the drug in pre-clinical models and dose ranges relevant to pharmacodynamic activities is necessary to determine early development risk (therapeutic window), to support a safe and appropriate Phase 1 dosing strategy (dose levels and escalation), and to ensure that the Phase ½ program investigates pharmacologically appropriate dose levels. Visit our services page to learn more about our capabilities and find out how Allucent’s nonclinical drug development experts can help you with designing and conducting pre-clinical studies.

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