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Chapter 4

Application of Pharmacokinetics in Early Drug Development

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Additional information is available at the end of the chapter

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Abstract

The intention of this chapter is to provide an overview of how pharmacokinetics, also termed PK, is applied in early drug development. While there are many readily available printed and web accessible sources on pharmacokinetics, its technical terms, model definitions, and calculation methods; how the science of pharmacokinetics is used in specific situations, namely early drug development are not as readily covered. In fact, the reader will see that the continual theme in this chapter is that a small amount of pharmacokinetic data and its interpretation in the first nonclinical or clinical study is important in obtaining additional pharmacokinetic, safety, and efficacy information for the next study. The role of PK in the three phases of clinical drug development is described as well as the types of early Phase 1 studies where PK determinations are important. The PK measurements in the first in humans study (FIH) provide a tentative confirmation of safety at the measured exposures from the tested dose levels. Even if exposures from a given dose change due to food-effects, drug–drug interaction, drug-disease interactions, or use in a special population, safety can be assessed by bridging these results to the initial safety or efficacy exposures.

Keywords: pharmacokinetics, drug development, compartmental modeling, non-compartmental pharmacokinetics, non-clinical pharmacokinetics

1. Introduction

The intention of this chapter is to provide an overview of how pharmacokinetics, also termed PK, is applied in early drug development. Since, PK is defined as the study of the effects of

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a living organism on an administered drug, the majority of pharmacokinetic studies involve the measurement of a specific compound in an easily sampled physiological fluid, like blood, plasma, serum and on occasion, in saliva. Excreted substances are also measured in urine or feces. In some rarer situations, measurements are made with more invasive sampling methods, such as a tissue biopsy, cerebral spinal fluid, bronchoalveolar lavage fluid, or middle ear effusion fluid. Regardless of the sample type, the measured concentrations are regarded as indicative of the concentrations at the specific site of action for the drug. Even excreted drug data can be used to describe the PK within the body; drug excretion rates into urine are recognized as proportional to plasma concentrations at midpoints of the collection interval, and amounts of drug in urine and feces can give some idea of excretion pathways. Series of drug concentrations measured in biological fluids over an adequate amount of time give the pharmacokinetic scientist a 'window' into the body, and by analyzing the time course of concentrations, information on the unseen drug in the various body compartments can be inferred. Thus, applied pharmacokinetics are useful in various types of pharmacological evaluations, be it for academic purposes, clinical research (inside and outside of drug development), or in clinical medicine (individualized dosing and therapeutic drug monitoring) [1–3].

While there are readily available printed and online materials on pharmacokinetic topics such as its technical terms, model definitions and calculation methods [4–5]; there are some gaps when it comes to how the science of pharmacokinetics is used in drug development. Several authors however, have touched on various aspects and a reader of this chapter may gain additional knowledge by consulting them [6–8]. Most healthcare workers and scientists are relatively familiar with the clinical pharmacology and medicine package inserts which include a pharmacokinetic section of an approved drug's labeling. This section of the package insert gives the general information that has been gleaned from large amounts of research and helps the practitioner or scientist understand the general absorption, distribution, metabolism, and elimination of a given therapeutic agent. In essence, this is only a short summary of what is known about this drug. Not readily apparent from the short summary is the role that pharmacokinetics had from the start of a drug's development through its approval journey. Through the application of pharmacokinetics, the maximum information can be extracted from data when only a few subjects are available as in a first in human (FIH) clinical study and then this information is applied to the design and interpretation of the next study during the drug's development phase. Furthermore, even before the first clinical human study is conducted, pharmacokinetic and toxicological data from animals can be used to predict human pharmacokinetics and to assist in the determination of a safe starting dose and the optimal study design. In fact, the reader will note that the continual theme in this chapter is that pharmacokinetic data and their interpretation in the first study is important in obtaining additional pharmacokinetic, safety, and efficacy information a subsequent study, and so on, throughout the drug development process. In the following pages, various types of PK evaluations and/or studies are described.

2. Pharmacokinetics and early drug development

Clinical drug development, meaning drug research in human subjects, is generally described in three phases, each comprised of a number of different clinical studies, Phases 1, 2, and 3, (see

Figure 1) [9, 10]. However these three phases do not encompass the entirety of the research for any given new drug: nonclinical research starts prior to Phase 1, and post-marketing studies (sometimes referred to as Phase 4) continue after Phase 3 and medicines regulatory agency's approval. Once a new chemical entity (NCE), a new molecular entity (NME), a new biological entity (NBE), a new active substance (NAS) or a new therapeutic entity (NTE) [11], also called investigational product (IP), or in general for this chapter, a new drug, is identified and the minimum *in vitro* and animal data are gathered, and after filing an application with the appropriate regulatory agency, a promising substance can start clinical research [12]. For sake of clarity, an overview of the three phases of studies is given below and the roles of PK data are highlighted.

Phase 1 studies (some exploratory studies are also called Phase 0) in clinical drug development are described as the initial introduction of the drug into humans, in small numbers of healthy subjects (if appropriate), starting at lower doses and escalating as safe to therapeutic ranges and super therapeutic ranges if possible. The reasons for studying higher doses, if deemed safe to do so, can be multi-faceted. Confirming safety at higher doses helps determine a margin of safety around the efficacious doses, and aids in determining the clinical relevance of any drug–drug- and drug-disease-interactions, or special population differences that may be elucidated later. Pharmacokinetics over a wider range leads to the ability to correlate drug effects (therapeutic or adverse) with drug exposure, and to characterize these relationships [13]. The aforementioned safety margin also allows the drug sponsor some flexibility in determination of the final marketed dose if necessary. Phase 1 also includes specific studies designed to study special populations, such as the elderly, children, in people

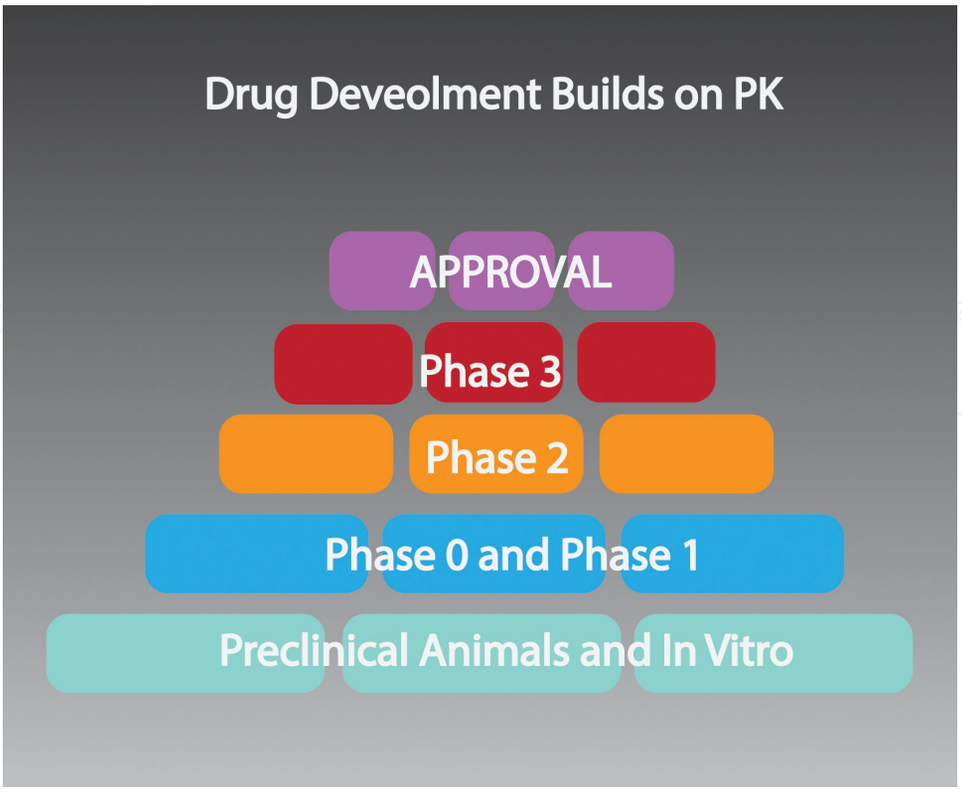


Figure 1. Phases of drug development built on pharmacokinetics.

with hepatic or renal impairment. In these studies, pharmacokinetic endpoints are the primary goal, allowing relatively small studies (low numbers of subjects) to inform the future Phase 2 and 3 studies and marketing after approval. The results of these studies are reflected in the approved drug's labeling, where warnings about the use in certain disease-states or dosage adjustments are communicated.

In Phase 2 studies of clinical drug development, the objective is not only to determine that a drug continues to be safe but that it remains to be safe when used in patients with the disease it is intended for to treat. The information gathered in Phase 2 serves the dual purpose of studying safety and efficacy while providing proof to the sponsor that the drug is worthy of further development. The pivotal Phase 2 study for continuation of Phase 2 and/or starting Phase 3 is often called 'Proof of Concept (POC).' The value of PK measurements in Phase 2 adds another layer of understanding how the body processes the drug; these studies determine differences in PK data between categories of patients, namely those with the targeted disease and normal healthy volunteers. Sometimes patients will have higher or lower exposures of a drug due to the difference in ability to absorb a drug, or the drug may be eliminated differently due to the disease state. In general, the more the patient is affected/weakened by the disease, the more PK will differ from healthy subjects. Knowledge of the PK in the patient population forms a bridge to knowledge of safety and perhaps efficacy gathered in Phase 1. Phase 2 PK facilitates any need for dose adjustments to achieve safety or efficacy. PK correlations with efficacy can begin in earnest once patient data is available; this data along with the Phase 1 data is modeled and simulations using those models assist in choosing the Phase 3 dose ranges.

Phase 3 in clinical drug development consists of several large studies in patient populations designed to collect further safety data, to observe possible adverse events which occur only rarely, to continue to evaluate efficacy and compare with current therapies for the indication, and to guide its use once approved and on the market. However, clinical research does not necessarily come to a halt at the end of Phase 3. After approval and marketing, additional studies may be run by the sponsor to establish marketing claims and to seek new indications. Adverse event data are continually collected to identify even rarer adverse events not uncovered in Phase 3. Phase 3 PK data is usually performed only as a few samples in many subjects or complete profiles in a subset of subjects; this data is for confirmatory purposes, used in correlation with efficacy or adverse events. This data is added to the ongoing modeling (discussed later in Section 3.1) to discern sources of variability in the PK data from the patient population.

The above descriptions of each phase of drug development may seem as though each phase precedes sequentially, one starting after the end of the other; however this may not always be the case. While typically the end of Phase 2 commences the beginning of Phase 3, the other phases may overlap in time. This is mainly to conserve research and development resources. For instance, the longer animal studies and reproductive toxicity studies may not run until the results are needed to support the Phase I and II studies for drugs that may require longer treatment durations or research in women of child-bearing potential (WOCBP), respectively

[14]. A thorough Phase I study to determine QTc prolongation and potential for cardiac arrhythmias (if not characterized already in earlier studies) should not be run until some idea of the clinical doses and exposures are determined and after a few studies have shown some promise for the drug's future approval.

3. Pharmacokinetic analyses

Pharmacokinetic analyses types can be broken into two general approaches: compartmental and non-compartmental. Non-compartmental analyses are a series of calculations that estimate the exposures and elimination properties of a drug with very few assumptions about the particular mechanisms involved. Non-compartmental exposure parameters (such as area under the concentration-time curve (AUC) and the maximum exposure (Cmax) can be calculated and are interpretable when no other PK information is available; these parameters indicate the amount of drug in the body and for how long it is there, and the peak concentration that is achieved.

Compartmental methods can be described as the determination of a mathematical expression, or model, which adequately describes the PK of a given drug. On the most basic level, these models consist of the mathematical description representing the body as one or a series of hypothetical volume compartments which drug distributes into and out of, or from which it is eliminated. These models not only describe the PK properties of a drug, but can be predictive of PK at different dose levels or administration conditions. Complex models aid in the elucidation of smaller processes which make up the PK in its entirety, such as the rate and capacity of the different metabolism pathways involved in a drug's elimination.

3.1. Compartmental pharmacokinetics

The process of fitting PK data to a given mathematical description, or model, is known as compartmental modeling. This modeling is carried out with specialized software applications and [15, 16] **Figure 2** shows the simplest one-compartment PK model where drug is introduced by an intravenous bolus injection into a representative volume compartment and the differential and integrated equations that can be fitted to actual data to determine the values of the constants as defined. Multiple-compartment PK models, such as a 2-compartment model, or a 3-compartmental model, commonly describe a concentration-time course adequately, but more complex models may contain more compartments. The mathematical models are based on the processes which move drug into or out of the compartments; these may be a constant rate of infusion or elimination (a zero-order kinetic process) or concentration-driven diffusion processes (first-order kinetics) or by saturable active transport or metabolic processes (Michaelis–Menten kinetics), or combinations thereof [17–19]. The intention of a compartmental model can be as straightforward as to find the simplest model which describes the PK and predicts drug exposures under new conditions, like a higher dose, or when administered in multiple doses over time, or when administered under a different route

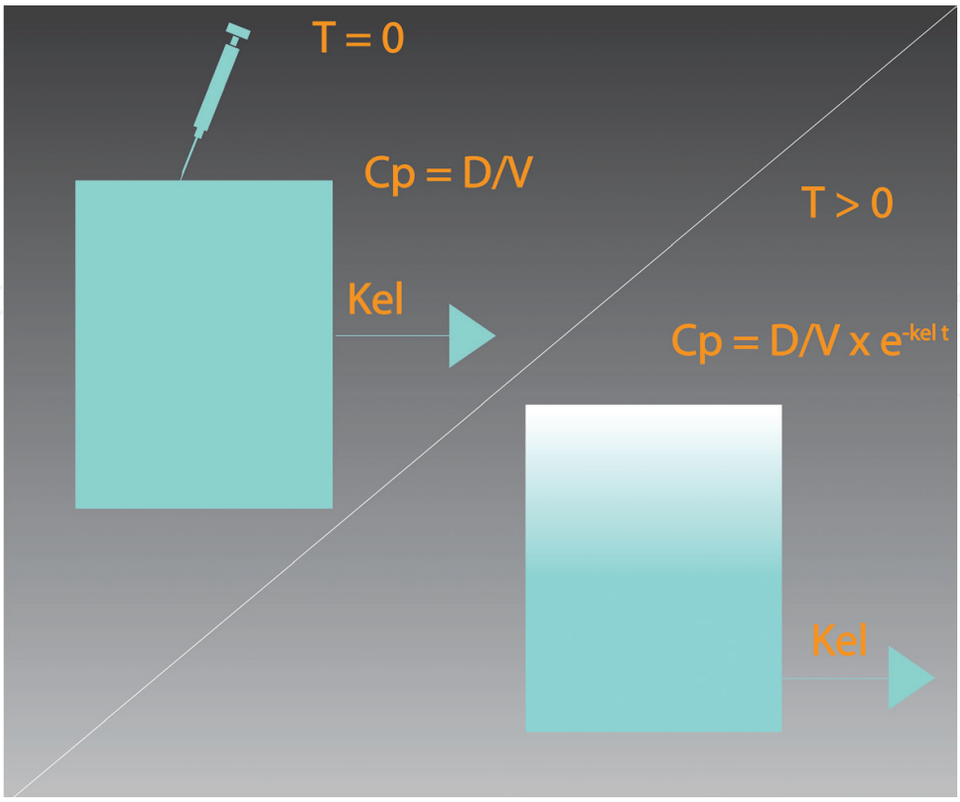


Figure 2. One-compartment pharmacokinetic model. graphic presentation of a one-compartment PK model with an intravenous bolus injection of dose (D) into a single central compartment of volume V, with a first-order elimination rate of kel. Where Cp is the concentration in the compartment which decreases over time (t). The model is described by a single differential (1) $dCp/dt = D/V \times (-kel)$. The integrated Eq. (2) is $Cp = (D/V)\, e^{-kelT}$. Secondary parameter CL (clearance) is calculated by Eq. (3) CL = V*kel.

of administration. However, sometimes the purpose may be more complex, to elucidate additional processes such as metabolism mechanisms or drug effects, and these models may contain many compartments.

Compartmental modeling in the very early stages of drug development might be used for supplemental information or to set the initial assumptions for further additional modeling later in the drug development program; known as population pharmacokinetics [20]. Population pharmacokinetics (termed in the industry as 'Pop PK') is the systemic analysis of compiled data from specific studies or from the entire drug development program. These analyses are used to better understand the concentration-time course of the drug and to explain potential sources of PK variability. These models take either sparse PK data (limited numbers of samples) from large numbers of subjects and patients, or both, and/or rich sampling data (full serial PK sampling profiles) from early PK studies, and often incorporate development of individual patient covariates (e.g., BMI, race, genotypes, concomitant medications, disease status, etc.) to predict exposure and effects in individual patients. **Figure 3** shows that this type of analysis not only allows individual patient predictions, but also provides average PK parameters for the population. A population PK approach is also useful in clinical research situations where

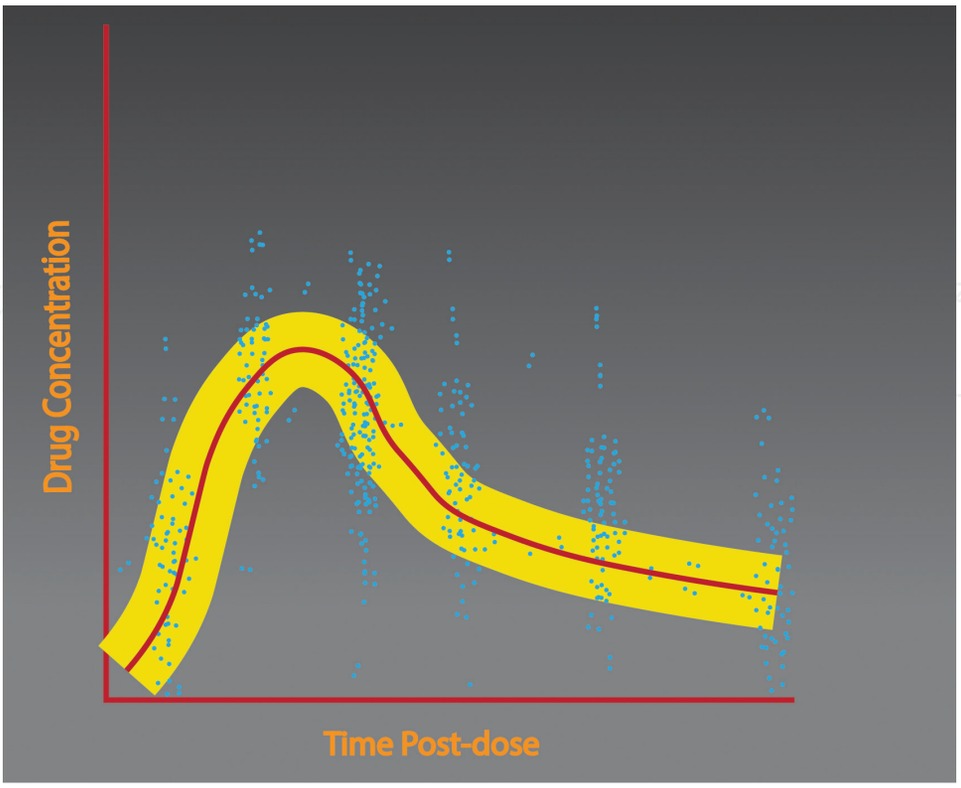


Figure 3. Population pharmacokinetics. Population model predictions (solid line) with 95% CI (shaded area) with observed data (circles).

ethics, patient safety, and/or patient comfort limit the number of PK samples that can be collected, such as in neonates, pediatrics, and patients with advanced diseased states.

Compartmental and non-compartmental (to be discussed Section 3.2) PK parameter estimates tend to vary within (intra-patient variability) and between individuals (inter-patient variability), with some drugs having more variability than others. Commonly these estimates vary by at least ±15–20% in normal volunteers which can make interpretations challenging, especially when only a few subjects have been evaluated. PK estimates in patient populations typically have even more variability. Population pharmacokinetics, once data is obtained in enough patients and subjects, can help identify and characterize the various sources of variability.

3.2. Non-compartmental pharmacokinetics

Non-compartmental pharmacokinetics include a number of calculations performed with a series of PK samples usually with plasma- or serum-concentration-time data. These parameters provide a model-free description of how the drug is dispersed and eliminated from the body. These types of analysis can be done very quickly with limited numbers of subjects, where in compartmental or population modeling can take quite some time to build a model. Since no assumptions of which type of compartmental model fits the data best are required, a non-compartmental approach is applied in most Phase I PK studies, and is quite useful in

understanding the drug and indexing its exposure, determining the clinical dose, and designing the final marketed dosage form. The PK parameters obtained from non-compartmental analyses are illustrated in **Figure 4**. Cmax, the peak concentration gives researchers a maximum drug exposure and is also dependent on the absorption rate for extravascular administrations, while the time of Cmax, Tmax, is also indicative of the rate of absorption, but one must understand drug elimination is also occurring at this time. The log-linear slope at the end of the concentration-time curve can be used to estimate the terminal elimination rate constant and the terminal elimination half-life, assuming the curve is well characterized and the PK exhibits first-order elimination. Too short of a sampling interval or limitations of the bioanalytical method may result in missing the terminal elimination phase, so in some cases this slope may be more representative of drug distribution. By calculating an area under the concentration-time curve, called AUC, an index of overall exposure is obtained, and this exposure is independent of the shape of the curve, be it the sharp increase of an intravenous injection with a high Cmax, or lower concentrations observed over a longer amount of time after a slow-release oral formulation. From AUC calculations and the terminal elimination rate constant, estimations volume of distribution and clearance, abbreviated as V and CL, for intravenous doses, or after extravascular doses abbreviated V/F and CL/F, unadjusted for the bioavailable, F, can be made.

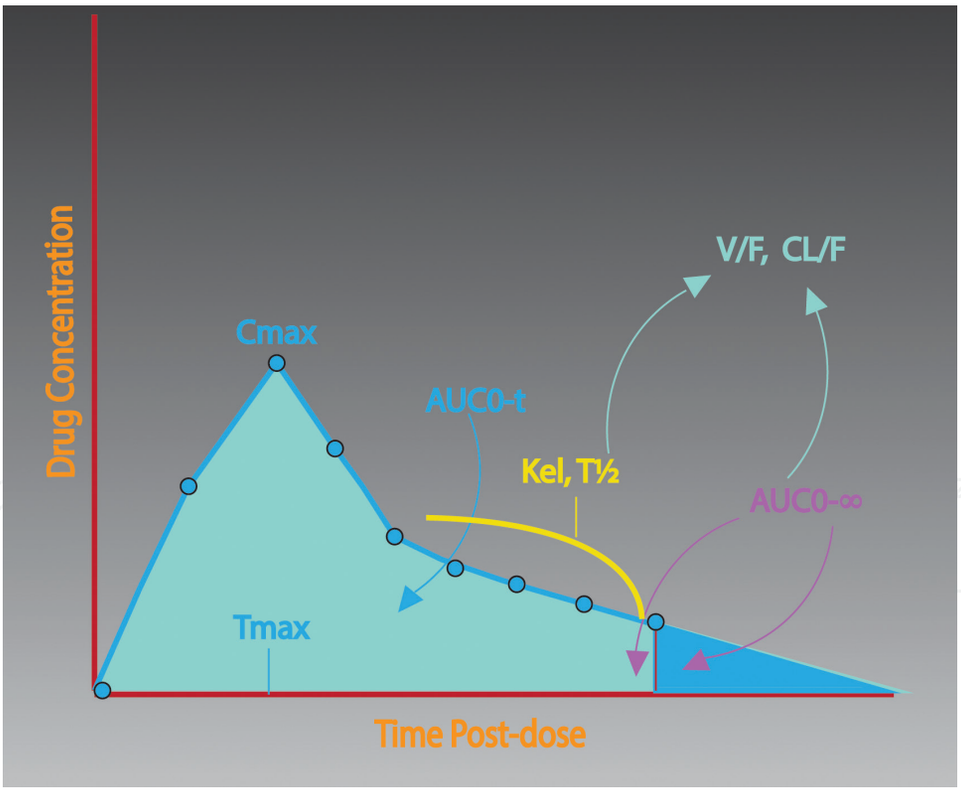


Figure 4. Non-compartmental model parameters. Cmax = peak concentration, Tmax = time of peak concentration, kel = negative terminal slope from ln concentration versus time regression, T1/2 = 0.693/kel (apparent terminal elimination half-life) AUC0-t = Area un the concentration-time curve from 0 to the last quantifiable concentration estimated by the trapezoidal rule, AUC0-∞ = Area under the curve extrapolated to infinity (AUC0-t + Cp(t)/kel, CL/F = Dose/AUC0-∞ (after a single dose), V/F = apparent volume of distribution after an extravascular dose, calculated by CL/F / kel.

4. Nonclinical pharmacokinetics

Before an investigational drug is ever administered to a human subject, an immense amount of animal and in vitro data are gathered. For example, tests in cell lines and/or animal models are used to determine the potential of the drug's therapeutic action. Other in vitro tests can screen for safety, such as in hERG (Human ether-a-go-go Related Gene) expressed cells, to determine a drug's potential to interact with the potassium channel, I_{KR}, and cause cardiac arrhythmias [21]. Ultimately, single- and repeat-dose toxicity studies, also called 'toxicokinetic or TK' studies, in rodents and at least 1 non-rodent species are needed to support the investigation of the drug in humans [14]. While these studies are mandated by regulatory agencies, they are also useful in the design of the FIH study for a drug's development program. Depending on the type of drug and its apparent risk, several methods of determining the starting dose based on observed toxicity at dose levels can be used. These methods range from simple adjustment and allometric scaling of the non- observed adverse effect level (NOAEL) in the most sensitive animal species studied, with a safety margin [22]. to complex scaling modeling to predict human exposures from animal data. For particularly risky compounds, the starting dose is sometimes carefully based on the minimum biologically active concentration and its associated dose level, also called the minimum effective dose (MED) [23].

Sometimes detailed PK in animals is available, but generally the PK data from animal studies come from the toxicoketinetic studies. In these studies, the goal is to determine exposure for correlation with toxicity, but qualitative expectations of how the drug will behave in a human are conceived. It would be expected, but not guaranteed, that a quickly absorbed and quickly eliminated drug would also act similarly in humans. Useful predictions of a drug's human PK can be made using computer modeling techniques, called PBPK (physiological based pharmacokinetic modeling) interspecies scaling, which take different species' capacities of absorption, body distribution, and metabolic/excretion into account and simulate PK concentrations based on an analogous human model [21, 24–26].

Nonclinical studies are also important for providing an idea of the mechanism of the drug's metabolism, whether any cytochrome P 450 enzymes are involved, and identification of metabolites which could be important in humans [27]. Metabolites identified in animals that represent 10% of drug circulating material need to be monitored in toxicology studies and later in clinical studies if still a significant metabolite, is disproportionately produced in humans, or if it is biologically active [28]. In vitro experiments with hepatic enzyme preparations and various chemical probes identify which CYP 450 enzymes are potentially active in the metabolism of a drug. Once these are determined, potential drug-drug interaction pathways are realized; this information is then used to design Phase I drug-drug interaction studies to characterize the clinical significance of these possible interactions in. In vitro experiments also provide the identities of drug-transporters which may move drug into or out of various organs in the body. Drug–drug interactions can also be mediated by inhibition or competition within these transporter systems [29].

5. Early clinical studies with primary endpoints of safety

Earlier this chapter described the primary objective of Phase I as determining safety in a small number of subjects before the introduction of the drug into patients. This remains true, but for the purposes of this chapter, Phase I studies will be described as studies whereby safety measurements are the primary endpoint (or finding) and where primary endpoints are PK-related.

5.1. First in human studies

The main purpose of the first in human clinical study (FIH) for a drug is to test that it is safe, meaning that subjects are monitored for signs of toxicity, especially those indicating risk of mortality or morbidity. Tolerability, the ability of a patient to use the drug for its intended indication, without unacceptable, non-life-threatening adverse events that would require discontinuation of treatment, is also an important consideration. Risk-to-benefit ratios are considered when determining the required tolerability and risks of toxicity; a drug for a life-saving, unmet clinical need, such as cancer, would be considered for approval even if it carries more risk than a drug for a self-limiting or non-life-threatening disease, such as the common cold. From the animal data discussed above, researchers have a good idea of the types of toxicity and at what exposures they may occur for a given drug, yet the first human study is critical in confirming the drug's potential for toxicity in a human. PK in a FIH is therefore very informative, telling us not just if toxicity occurs, but at what exposure that toxicity correlates with.

5.2. Single-ascending-dose studies (SAD)

Typically, the FIH study is the single-ascending dose study, where small numbers of subjects are dosed carefully with either the drug or placebo, and safety is monitored by recording adverse events, clinical laboratory measurements, vital signs, electrocardiograms, and additional tests depending on concerns raised in the animal studies or from the known pharmacology. Once a small dose is administered and considered to be safe, then a higher dose (typically 2–3 times higher than the starting dose) is administered to a new group of subjects which is then considered before a higher yet dose is given. The escalation schedule for ascending doses needs to be considered carefully, using smaller increments of increase with higher risk drugs, the predicted therapeutic range for the drug, and the levels of exposure where toxicity was seen in animals [30]. Study protocols for drugs considered to be high risk or of narrow therapeutic range may have stopping criteria based on PK as well as safety. Some study protocols will set an upper limit on PK parameters of exposure that are not to be exceeded in the study. The escalation schedule or planned doses may be revised depending upon the outcome of the previously dosed groups. Unexpected toxicity may require lowering the dose and subsequent doses; lower than expected exposure (if assessed before the study finishes) might require increasing the planned doses or accelerating the dose escalation.

The design of the FIH study will incorporate animal data or interspecies scaling predictions to determine when and how long blood (usually plasma or serum) should be sampled for PK measurements. Ideally, to characterize a PK profile, sampling would be optimized

to capture absorption rates, peak concentrations, distribution and elimination phases, and would minimally be 2–3 times the elimination half-life, preferably 4–5 times the elimination half-life. Sometimes at lower dose levels this is difficult due to the limitation of the bioanalytical method used to measure drug concentrations.

When PK information is needed for dose escalation a common practice is to perform interim PK analyses as the study progresses, where the PK is examined in one group before proceeding to the next higher dose level group. This is a time sensitive process where careful planning with logistics between the clinic conducting the study, sample shipment, the laboratory analyzing the samples, the scientist performing the PK calculations, and sometimes a data safety monitoring board (DSMB) who will review the data and make a determination along with the sponsor and principal investigator in charge of clinic conduct. Once at least two dose levels have been administered, the scientist will use the data obtained to date in order to determine if the increase in exposure is proportional to the increase in dose (dose proportionality) and if so to predict what exposures might be at the next dose level, given that dose proportionality continues to the next dose. If dose proportionality is not seen (the PK may be described as 'nonlinear') [31], and the increase is higher than proportional to the increase in dose, escalation to higher dose levels should proceed with caution, as saturation of a metabolic or elimination pathway could lead to sharp increases in PK concentrations with only a small increase in dose. If PK concentrations are less than proportional to the increase in dose, indicating a saturation in the absorption process, then the dose escalation schedule may need to be revisited in order to achieve target exposures.

5.3. Multiple-ascending-dose studies (MAD)

PK information gained in the single-ascending dose assessment of a drug development program is used further in the design of the next clinical study, which for most drugs is the multiple-ascending dose study. Because most drugs need to be given repeatedly over time, safety information for continuous use is needed. In this study, the drug is administered for the number of doses required (based on the single-dose PK) to reach steady-state levels, the highest exposure a given drug regimen will achieve, where the given drug exhibits first-order elimination (**Figure 5**). Again, the main purpose of the study is to determine safety at maximum exposures, but PK at these exposures is applicable to the design of the next study in the drug development program. Steady-state levels depend upon the half-life, the dose, and how often the drug is given (also called the frequency of administration). If PK properties after a single dose are known, then the number of repeated doses given at equal intervals for a duration of approximately 5 times the half-life will reach predictable steady-state levels. Confirmation of steady-state in this type of study is usually assessed by determining if trough (predose) concentrations for the last few doses are approaching a constant value; [32] this also helps confirm that the half-life observed after single doses was based upon the elimination phase, that the PK is indeed first order, and is or is not 'linear' over time. Linear or nonlinear, the single- and multiple-dose studies in Phase I not only determine safety at a certain exposure, but the relationship of dose to exposure, leading to predictability to adequately achieve target exposures further along in Phases II and III.

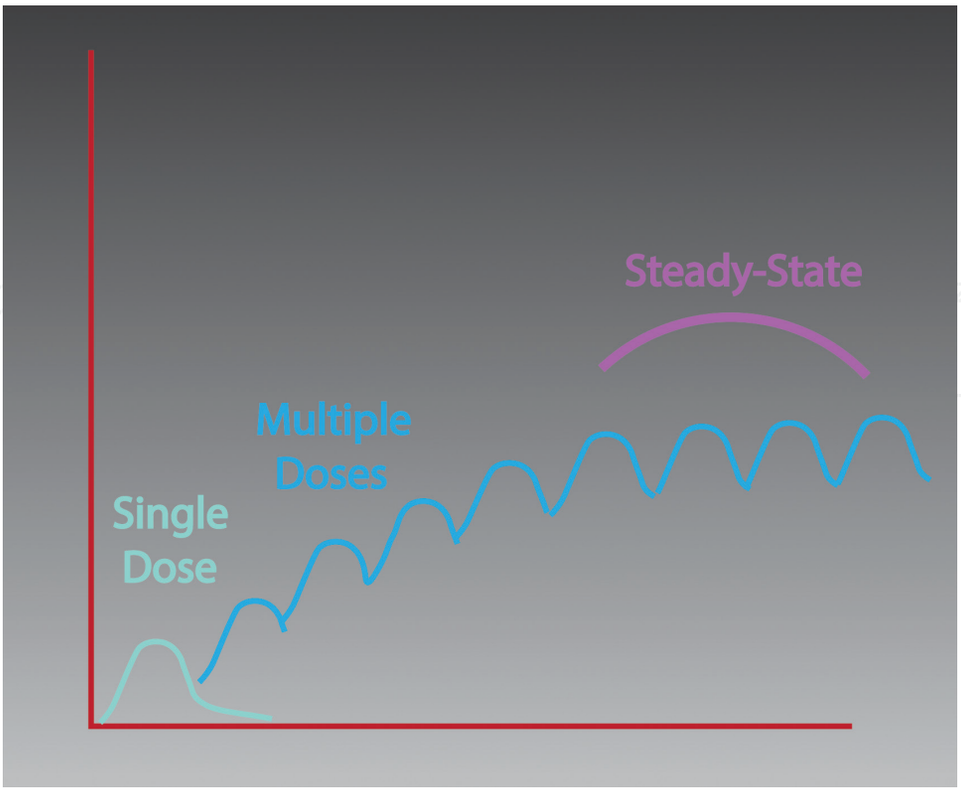


Figure 5. Single dose and steady-state pharmacokinetics.

It should be noted that the single- and multiple-dose studies are not always run in two separate studies. Depending upon the sponsor, type of drug, its PK qualities, and how much dose-limiting toxicity is expected, these assessments may all be performed under a single study protocol [33]. These studies are termed SAD/MAD studies, and may be designed in two parts, a single-dose and a multiple-dose part to follow when the first is completed or partially completed. Sometimes the study is designed for the sequential groups to get a single dose followed by a washout period where they are monitored, and then the same group will be started on multiple doses at the same level as the first dose for a period of time expected to reach steady state. Safety and or PK is examined for that group, and if deemed safe, then the dose is escalated in the next group.

6. Early clinical studies with primary PK endpoints

Once the SAD and MAD studies have confirmed acceptable safety to proceed further into Phase 1, several types of studies are conducted where PK endpoints are the primary objective, and continued collection of safety data is only secondary. These studies determine the effects of other drugs, diseases, and patient qualities on the PK of the drug in relatively small numbers of subjects, reducing the risk to patients in the Phase 2 and 3 studies, and ultimately informing the marketed use of the drug.

6.1. Food effect studies

One of the most important PK studies for an orally administered (and sometimes with inhaled drugs where some drug is swallowed) is the food-effect study. An experienced clinical pharmacokineticist will say that the absence of a food effect on the rate or extent of a drug's absorption is rare, and looking at many drugs, most have some difference in absorption between fed and fasted states. Food-effect information is typically not clear from nonclinical studies in most programs, as animals are usually fed ad libitum or on a regular schedule in toxicology studies. A food effect can be somewhat predicted for a specific drug, with knowledge of its solubility, its lipophilicity, and pH dependence on ionization and partitioning, but a human study is required to confirm the extent of the food-effect [34]. Since food in the stomach can affect gastric pH and potentially bind to a drug, and food and/or its fat content can affect gastric emptying time, the probability of some effect on absorption is high. A food effects range from very subtle changes in just Tmax or Cmax, to several-fold increases or decreases in overall exposure, to ultimately where a lipophilic drug might be totally unabsorbed without a minimum of dietary fat. PK parameters, especially Cmax, Tmax, and AUC, can characterize this difference with only a single dose of drug, in a crossover study design, where each subject is administered the drug with and without food. Many drug development programs strive to get this information as early as possible to determine the optimal dosing conditions, and is often part of the SAD, MAD, or SAD/MAD study protocol.

The purpose of the food-effect PK study is to determine if a difference occurs, and if this difference is clinically significant. If found to be clinically significant, that is that food decreases absorption enough to make it less effective, or that it increases absorption enough to cause toxicity. If the PK shows a clinically significant food effect, adjustment of the therapeutic dose and/or instructions on how the drug should be administered will be included in the approved drug labeling. The type of drug is also important in this decision, as commonly food may delay Tmax and decrease Cmax, but if only the extent of exposure (AUC) is important for the drug's efficacy, then the food effect might not be clinically relevant.

6.2. PK studies in special populations

Once the pharmacokinetic behavior of a drug and its initial safety is confirmed in normal healthy volunteers in the early Phase 1 studies, additional Phase 1 studies are performed to determine if PK differs in various special populations [35]. A simple special population study can be used to bridge the entire drug development program of a drug for one population to apply to another population. An example would be a drug developed in Japanese populations that is then intended to also be marketed in the US. Most small molecule drugs are investigated in subjects with hepatic or renal impairment [36, 37], and depending on the drug's intended use, additional studies in elderly, obese, certain racial/ethnic groups, or others are performed. While safety is monitored in these studies, the PK endpoints allow inference of safety and efficacy that has been determined in previous studies. In other words, if age does not appear to affect the PK of a drug, it is well accepted that the previous safety findings will also likely apply, in general, if the drug is used without regard to age. In hepatic and renal impairment, plasma proteins, such as albumin, can be lower than in healthy subjects, so free drug

concentrations are often examined to determine if any PK differences are related to the differences in binding, or if increased free drug concentrations might result in any drug effect differences [38]. These studies are often single-dose PK studies in the special group and in healthy volunteers of similar demographics. PK parameters of exposure are key in the between-group comparisons; however, elimination rates and absorption rates are also important.

6.3. Drug-Drug interaction studies

As mentioned previously, nonclinical studies are key in screening a drug for potential drug–drug interactions (DDIs). Once the cytochrome P450 enzymes and transporters for which a new drug is a substrate, an inhibitor, or can induce expression, are identified, clinical studies are performed to confirm, quantitate, and determine clinical significance of any DDI. It would be tedious and cost prohibitive to test every possible DDI, so appropriate probes [39] (other drugs which are known CYP or transporter substrates, inhibitors, or inducers) are chosen to be co-administered and PK measured to determine if a clinically relevant DDI through a specific metabolism or transporter pathway exists [40]. Without PK measurements in this type study, it would take large numbers of subjects to study a drug–drug interaction with safety endpoints only, however with PK, a small number of subjects' exposures to one or both drugs can determine if there is a safety risk by examining previous PK measurements and correlated safety findings. These study designs may differ depending upon the potential interaction, but usually the drug under development is dosed to steady-state at a therapeutic dose. Often these studies are conducted with 12–24 healthy subjects confined to a research clinic, and consist of a fixed treatment sequence for all subjects. An example of a common design would be where the probe drug is administered alone, followed by a washout period, then the multiple doses of the investigational drug are given until steady-state levels are reached, then the probe drug is co-administered. PK of the probe drug is measured to determine if the PK is affected. The sequence could be reversed if the investigational drug is hypothesized to be affected by the probe drug. Two-way DDI designs are also used to determine the two drugs affect each other. The primary PK endpoints are generally Cmax and AUCs to determine if peak or overall exposure differ due to a DDI, but Tmax and elimination rates are helpful in determining if the mechanism is due to decreased metabolism or a change in absorption.

Interpretation of the PK data for these studies is often straightforward; if a DDI increases exposure of a drug, depending upon its safety profile, to a degree that toxicity could develop, or decreases exposure enough that efficacy would be lost, then warnings will be issued in the approved labeling. Occasionally unexpected results in these studies are seen such that relating the results to specific enzymes or transporters becomes difficult, especially when multiple enzymes or unknown transporters are involved. In such instances, the characterization of DDIs helps in the design of Phase 2 and 3 studies where a study protocol excludes patients taking certain medications, and allow the safe investigation in patient populations.

6.4. Radiolabeled drug studies

A concern for a small molecule drug in development is the question of whether the drug is readily removed from the body completely, and how that complete elimination occurs. Less

so is whether the drug might accumulate in specific tissues in an undesired way. Along with the question of how a drug is eliminated, another question is what metabolites are formed and how are they excreted. These questions are answered with PK studies using radiolabeled drug, which is commonly called the 'ADME' or 'Mass Balance' study [41]. These studies usually include only 6–8 healthy males given a single dose and confined to a research clinic until most of the drug-related radioactivity has been recovered in urine and/or feces. An easily measurable dose of the study drug is administered along with a small amount of the drug that is radiolabeled, usually with carbon 14 (^{14}C), and sometimes with tritium (^{3}H). PK of unlabeled drug and radioactivity in blood and plasma are measured, and total radioactivity are measured in complete urine and feces collections. These studies can be quite long, as the measurements continue and subjects are confined until only small amounts of radioactivity are excreted in urine/feces each day. The advantage of measuring radioactivity is that it represents the total amounts of drug-related material in blood/plasma, urine, and feces. The drawback for total radioactivity measurements is that it is non-specific. However, comparing unlabeled unchanged drug levels and total radioactivity levels allows the scientist to gauge the amount of metabolites that are circulating and their collective PK behavior. A second aspect of these studies are the determination of the identity of the metabolites and their quantities in plasma, urine and feces by radio chromatography, also known as metabolic profiling. Since the drug was radiolabeled, different chemical entities resulting from the breakdown of the drug in the body can be identified as they will also be radiolabeled. The amounts of radioactivity recovered in urine and feces are totaled, and summed, for the determination of mass balance, i.e. the amount of radioactivity administered is expected to be nearly equal to the radioactivity excreted.

The distribution of the drug and its metabolites (as measured by radioactivity) into erythrocytes is another important aspect of the ADME study, and goes along with the question of drug accumulating in tissues. By measuring radioactivity concentrations in whole blood and in plasma, it is possible to determine if the drug-related material binds to or collects in erythrocytes [42].

7. Summary

The above overview has shown that pharmacokinetics is an integral part of drug development, and a critical part of early drug development. At the beginning of Phase 1 in the development program only animal data is available; hence, what is known through pharmacokinetic measurements in those animal studies is applied in designing Phase 1 human studies. This chapter outlined the importance of pharmacokinetic data in drug development overall and in specific types of early clinical studies. The PK measurements in the FIH study provide confirmation of safety at the measured exposures from the tested dose levels. Even if exposures from a given dose change due to food-effects, drug–drug interaction, drug-disease interactions, or use in a special population, safety can be associated and risks assessed by bridging these results to the initial safety or efficacy exposures. Throughout the drug development program, pharmacokinetics is a tool used to link exposure to efficacy and safety, and it assists in the determination of dosages of marketed drugs; for this reason, PK data are an important part of the information provided to clinicians.

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