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CLINICAL PHARMACOKINETICS CONCEPTS IN THE DRUG DISCOVERY AND DEVELOPMENT PROCESS OF PHYTOMEDICINES IN SOME DEVELOPING COUNTRIES

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ABSTRACT
Clinical Pharmacokinetics can be defined as the study of the relationship between drug dosage regimens and the concentration time profiles. There has been in the last decades a significant progress in the field of Clinical Pharmacokinetics (CPK) in the drug development process and the understanding of the ethical and regulatory demands within the pharmaceutical industries. The three basic parameters that govern PK relationships are Clearance i.e. the volume of the blood that is cleared out completely of the drug per unit time, Distribution volume i.e. the apparent volume in which the drug has been distributed to make the measured concentration and half-life i.e. the time that is required for 50 percent of the drug to be completely eradicated. The knowledge of clearance can be useful in calculating the dose rate needed to retain a target concentration. In addition, elimination half-time helps in determining the time needed for a drug to be completely eliminated from the body. It also indicates the time taken to attain a steady state and can be further used to determine the optimum dosage interval for producing the target peak to trough. On similar lines, essential advancement has been made in the rational design of quinine dosage regimens for patients in places such as Africa and South East Asia. This review paper attempts to discuss ethical issues in clinical Pharmacokinetics in the development of new drugs for poverty related diseases in developing economies. The paper attempts to give an overview of the effect of pharmacokinetics as a factor on therapeutic failure, and how PK can support therapeutic drug monitoring in a clinical setting and its relevance in herbal medicines research. The ethical issues involving PK studies have been discussed.

KEYWORDS: Clinical, pharmacokinetics, pharmacodynamics, phytomedicines, drug discovery/development.

INTRODUCTION

Pharmacokinetics is defined as the study of the time course of drug absorption, distribution, metabolism, and excretion.[1] Clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.[1,2] The goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient's drug therapy.[2] The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations.. A drug's effect is often related to its concentration at the site of action, so it is necessary to monitor this concentration. Receptor sites of drugs are generally not accessible to drugs in some cases or are widely distributed in the body, and therefore direct measurement of drug concentrations at these sites is not practical. For instance, the receptor sites for a neoplastic drug like digoxin have been shown to be within the myocardium, and drug concentration cannot be directly sampled in this tissue. However, it is possible to measure drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids.[3]

The success of drug therapy is highly dependent on the choice of the drug and drug product and on the design of the dosage regimen. The choice of the drug and drug product, e.g., immediate release versus modified release, is based on the patient's characteristics and the defined pharmacokinetics of the drug.

A properly designed dosage regimen tries to achieve a specified concentration of the drug at a receptor site to produce an optimal therapeutic response with minimum

adverse effects. Individual variation in pharmacokinetics makes the design of dosage regimens difficult.[4]

The principles of clinical pharmacokinetics in the research and development of new drugs through the regulated drug development process in a developing economy is still at its infancy. There are so many factors that make PK research challenging in the developing countries, such as limited standardized bio analytical services, lack of or inefficient drug regulatory bodies, poorly organized ethics communities or Institutional review boards to censor medical research and in particular clinical trials. Some countries have made more efforts than others in promoting research ethics and drug regulation in their regions.

Personalized Drug Dosage Regimens

In general not all drugs require strict individualization of the dosage regimen. Most drugs have a large margin of safety with a wide therapeutic window, and strict individualization of the dose is not necessary.[5] Drug dosage regimens take into consideration race, age, weight and genetics.[5,6] The U.S. Food and Drug Administration (FDA) have approved an over-the-counter (OTC) classification for drugs that the public may buy without prescription. In the past few years, some prescription drugs, such as omeprazole, naproxen, and ibuprofen have been approved by the FDA for OTC status.[6] These OTC drugs and certain prescription drugs, when taken as prescribed, are generally safe and effective for the labeled indications without medical supervision.

For drugs with a narrow therapeutic window, such as digoxin, anticonvulsants, and some anti-asthmatics, such as theophylline, individualization of the dosage regimen is very important. The objective of the dosage regimen design for most drugs is to produce a safe plasma drug concentration that does not exceed the minimum toxic concentration or fall below a critical minimum drug concentration below which the drug is not effective.[6] For some drugs like phenytoin which follow nonlinear pharmacokinetics at therapeutic plasma drug concentrations, a small change in the dose may cause a significant increase in the therapeutic response, leading to potential adverse effects.

It has been shown that the monitoring of plasma drug concentrations is only valuable if a relationship exists between the plasma drug concentration and the desired clinical effect or between the plasma drug concentration and an adverse effect.[6] For some drugs in which plasma drug concentration and clinical effect are not related, other pharmacodynamic parameters may be monitored.

Importance of Therapeutic Drug Monitoring

The usefulness of a plasma drug concentration data can be based on the concept that pharmacologic response is closely related to drug concentration at the site of action. Some drugs, studies in patients have provided vital information on the plasma concentration range that is safe and effective in treating specific diseases within the therapeutic range, where the desired effects of the drug are seen.[3,6]

There are no absolute boundaries that separate sub therapeutic, therapeutic, and toxic drug concentrations. A gray area usually exists for most drugs in which these concentrations overlap due to variability in individual patient response.[3,5] Both pharmacodynamic and pharmacokinetic factors contribute to this variability in patient response.[7] The pharmacokinetics of a drug determines the blood concentration achieved from a prescribed dosing regimen. It is generally assumed that after continued drug dosing, the blood concentration will mirror the drug concentration at the receptor site, and it is the receptor site concentration that should principally determine the intensity of a drug's effect.[2,8] Consequently, both the pharmacokinetics and pharmacologic response characteristics of a drug and the relationship between them must be understood before predicting a patient's response to a drug regimen.[4]

Many pharmacokinetic factors cause variability in the plasma drug concentration and, consequently, the pharmacologic response of a drug. These factors include:

i. Disease states or physiologic states (e.g., extremes of age) that alter drug absorption, distribution, or elimination, (ii). Differences in an individual's ability to metabolize and eliminate the drug (e.g genetics, (iii). Drug interactions and (iv). Variations in drug absorption.

Variability is mostly attributed to factors influencing drug absorption, distribution, metabolism, or excretion. Disease states (e.g., renal or hepatic failure) and other conditions (e.g., obesity and aging) that may alter these processes must be considered for the individualization of drug dosage regimens (dose and frequency of dosing).[9] Therapeutic drug monitoring is defined as the use of assay procedures for determination of drug concentrations in plasma, and the interpretation and application of the resulting concentration data to develop safe and effective drug regimens.[1,10] If performed properly, this process allows for the achievement of therapeutic concentrations of a drug more rapidly and safely than can be attained with empiric dose changes. Together with observations of the drug's clinical effects, it should provide the safest approach to optimal drug therapy.[5]

The major potential advantages of therapeutic drug monitoring include maximization of therapeutic drug benefits as well as minimization of toxic drug effects. Therapeutic drug monitoring may be used in designing safe and effective drug therapy regimens.[11]

Some drugs are mandatory for clinical pharmacokinetic monitoring because their concentrations in plasma correlate well with pharmacologic response, for other

drugs, this approach is not valuable. For example, it is advantageous to know the plasma theophylline concentration in a patient receiving this drug for the management of asthma. Because plasma theophylline concentration is related to pharmacologic effect, knowing that the plasma concentration is below the therapeutic range could justify increasing the dose. However, it is of little value to determine the plasma concentration of an antihypertensive agent, as it may not correlate well with pharmacologic effects and the end-point of treatment, blood pressure, is much easier to measure than the plasma concentration.[3]

Therapeutic monitoring using drug concentration data is valuable when:

1. A good correlation exists between the pharmacologic response and plasma concentration. Over at least a limited concentration range, the intensity of pharmacologic effects should increase with plasma concentration. This relationship allows us to predict pharmacologic effects with changing plasma drug concentration.
2. Wide inter subject variation in plasma drug concentrations results from a given dose.
3. The drug has a narrow therapeutic index (i.e., the therapeutic concentration is close to the toxic concentration).
4. The drug's desired pharmacologic effects cannot be assessed readily by other simple means (e.g. blood pressure measurement for anti-hypertensive). The value of therapeutic drug monitoring is limited in situations in which: 1. there is no well-defined therapeutic plasma concentration range. 2. The formation of pharmacologically active metabolites of a drug complicates the application of plasma drug concentration data to clinical effect unless metabolite concentrations are also considered
5. Toxic effects may occur at unexpectedly low drug concentrations as well as at high concentrations.
6. There are no significant consequences associated with too high or too low levels. The therapeutic range for a drug is an approximation of the average plasma drug concentrations that are safe and efficacious in most patients.[6] When using published therapeutic drug concentration ranges, such as those in table 1. The clinician must realize that the therapeutic range is essentially a probability concept and should never be considered as absolute values. The therapeutic range of commonly monitored drugs is illustrated in table 1 for drugs such as carbamazepine, gentamicin, vancomycin etc.

Table 1: Therapeutic Range for Commonly Monitored Drugs.[11]

Monitored Drugs	Dose Range
Carbamazepine	4–12 µ g/Ml
Gentamicin	5–10 µg/mL
Tobramycin	5–10µg/mL
Valproic acid	50–100 µ g/mL
Vancomycin	20–40 µg/mL
Lidocaine	1–5 µg/mL
Digoxin	1–2 ng/mL
Amikacin	20–30 µg/mL

In administering potent drugs to patients, the physician must maintain the plasma drug level within a narrow range of therapeutic concentrations. Various pharmacokinetic methods may be used to calculate the initial dose or dosage regimen.

Due to inter patient variability in drug absorption, distribution, and elimination as well as changing pathophysiologic conditions in the patient, therapeutic drug monitoring (TDM) or clinical pharmacokinetic (laboratory) services (CPKS) have been established in many hospitals to evaluate the response of the patient to the recommended dosage regimen. The improvement in the clinical effectiveness of the drug by therapeutic drug monitoring may decrease the cost of medical care by preventing untoward adverse drug effects.[12]

Clinical Development

The success of drug therapy is highly dependent on the choice of the drug, the drug product, and the design of the dosage regimen. The choice of the drug is generally made by the physician after careful patient diagnosis and physical assessment. The choice of the drug product (eg, immediate release vs modified release) and dosage regimen are based on the patient's individual characteristics and known pharmacokinetics of the drug. Ideally, the dosage regimen is designed to achieve a desired drug concentration at a receptor site to produce an optimal therapeutic response with minimum adverse effects. Individual variation in pharmacokinetics and pharmacodynamics makes the design of dosage regimens difficult. Therefore, the application of pharmacokinetics to dosage regimen design must be coordinated with proper clinical evaluation of the patient.[6,13]

Medication Therapy Management **(MTM)** was officially recognized by the US Congress in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.[1] The objective of this act is to improve the quality, effectiveness, and efficiency of healthcare delivery including prescription drugs. An MTM program is developed in cooperation with pharmacists and physicians to optimize therapeutic outcomes through improved medication use. MTM provides consultative, educational, and monitoring services to patients to obtain better therapeutic outcomes from medications by the enhanced understanding of

medication therapy, improved compliance, control of costs, and prevention of adverse events and drug interactions. MTM programs have been developed for specific practice areas such as elderly care, diabetes, and asthma.[1,14,15]

Not all drugs require rigid individualization of the dosage regimen. Many drugs have a large margin of safety (ie, exhibit a wide therapeutic window), and strict individualization of the dose is unnecessary. For a number of drugs generally recognized as safe and effective (GRAS), the US Food and Drug Administration (FDA) has approved an *over-the-counter* (OTC) classification for drugs that the public may buy without prescription.[3,15] The objective of the dosage regimen design is to produce a safe plasma drug concentration that does not exceed the minimum toxic concentration or fall below a critical minimum drug concentration below which the drug is not effective. For this reason, the dose of these drugs is carefully individualized to avoid plasma drug concentration fluctuations due to inter-subjective variation in drug absorption, distribution, or elimination processes. For drugs such as phenytoin, a critical-dose drug that follows nonlinear pharmacokinetics at therapeutic plasma drug concentrations, a small change in the dose may cause a huge increase in the therapeutic response and possible adverse effects.[16,17]

Pharmacokinetics model for drug development process

Pharmacokinetic properties of drugs may be affected by elements such as the site of administration and the route of administered drug. These may affect the absorption rate.[2,7] Pharmacokinetics is often studied in conjunction with pharmacodynamics, the study of a drug's pharmacological effect on the body. Pharmacokinetics may be simply defined as what the body does to the drug, as opposed to pharmacodynamics which may be defined as what the drug does to the body.[9,17] The demonstration of the kinetic principles is shown in Figure 1, illustrating the graphical demonstration of the Michaelis Menten kinetics model which defines the relationship between an enzyme and a substrate as one of the pharmacokinetics parameters in clinical studies, where the substrate is a pharmaceutical drug.[19]

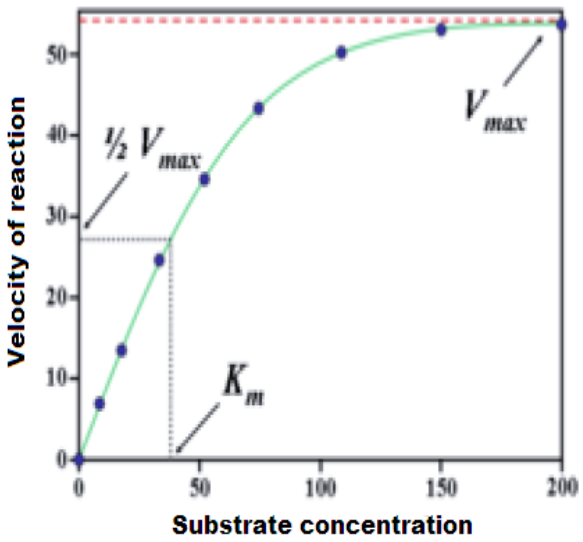

Figure 1: Shows graphical demonstration of the Michaelis-Menten kinetics model defining the relationship between an enzyme and a substrate as one of the pharmacokinetics parameters in clinical studies, where the substrate is a pharmaceutical drug.[19]

A number of different models have been developed in order to simple conceptualization of the many processes that take place in the interaction between an organism and a drug. One of these models, the **multi-compartment model**, gives the best approximation to reality, however, the complexity involved in using this type of model means that **monocompartmental models** and above all **two compartmental models** are the most frequently used. The various compartments that the model is divided into, is commonly referred to as the ADME scheme (also referred to as LADME if liberation is included as a separate step from absorption).[4,20]

The following pharmacokinetics parameters are studied for any potential animal and clinical drug development model.

Liberation - The process of release of a drug from the pharmaceutical formulation also associated to in vitro in vivo correlation.[5,7]

Absorption - The process of a substance entering the blood circulation.

Distribution - The dispersion or dissemination of substances throughout the fluids and tissues of the body.

Metabolization (or biotransformation, or inactivation) – the recognition by the organism that a foreign substance is present and the irreversible transformation of parent compounds into daughter metabolites.

Excretion - the removal of the substances from the body. In rare cases, some drugs accumulate in body tissue.

The two phases of metabolism and excretion can also be grouped together under the title elimination. The study of these distinct phases involves the use and manipulation of basic concepts in order to understand the process dynamics.[21] For this reason in order to fully comprehend the *kinetics* of a drug it is necessary to have detailed knowledge of a number of factors such as: the properties of the substances that act as excipients, the characteristics of the appropriate biological membranes and the way that substances can cross them, or the characteristics of the enzyme reactions that inactivate the drug.[22]

All the PK concepts can be represented through 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.[1,23] We can have the following representations as the **acid dissociation constant (pKa),** bioavailability and solubility, absorption capacity and distribution in the organism.[2,9,24]

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. In table 2 have been illustrated the most commonly measured PK metrics, through the characteristics such as dose, dosing interval, Cmax, Tmax etc.[1,7]

Table 2: The following are the most commonly measured pharmacokinetic metrics.[7]

Characteristic	Description	Example value	Symbol
Dose	Amount of drug administered	500 mg	D
Dosing interval	Time between drug dose administrations	24 h	τ
C_{max}	The peak plasma concentration of a drug after administration	60.9 mg/L	Cmax
t_{max}	Time to reach C_{max}	3.9 h	Tmax
C_{min}	The lowest (trough) concentration that a drug reaches before the next dose is administered	27.7 mg/L	C min/sec
Volume of distribution	The apparent volume in which a drug is distributed (i.e., the parameter relating drug concentration to drug amount in the body).red.	6.0 L	Vd=D/C0
Concentration	Amount of drug in a given volume of plasma	83.3 mg/L	Co, Css = D/Vd
Elimination half life	The time required for the concentration of the drug to reach half of its original value.	12 h	$t_{1/2}=\ln(2)/k_e$
Elimination rate constant	The rate at which a drug is removed from the body	0.0578 h^{-1}	$K_e=\ln(2)/t_{1/2}= CL/Vd$
Infusion rate	Rate of infusion required to balance elimination.	50 mg/h	**Km= Css.CL**
Area under the curve	The integral of the concentration-time curve (after a single dose or in steady state).	1,320 mg/L·h	$AUC_{0-\infty} = \int_0^{\infty} C\,dt$
Clearance	The volume of plasma cleared of the drug per unit time.		$AUC_{r,ss} = \int_t^{t+\tau} C\,dt$
		0.38 L/h	**CL**= Vd.Ke= D/AUC
Bioavailability	The systemically available fraction of a drug.	0.8	$f = \frac{AUC_{po} \cdot D_{iv}}{AUC_{iv} \cdot D_{po}}$
Fluctuation	Peak trough fluctuation within one dosing interval at steady state	41.8 %	$\%PTF = \frac{C_{max,ss} - C_{min,ss}}{C_{av,ss}} \cdot 100$ Where $C_{av,ss} = \frac{1}{\tau} AUC_{\tau,ss}$

In pharmacokinetics, *steady state* refers to the situation where the overall intake of a drug is fairly in dynamic equilibrium with its elimination. In practice, it is generally considered that steady state is reached when a time of 4 to 5 times the half-life for a drug after regular dosing is started.[24] The graph showing a model time course of drug plasma concentration that illustrates the main pharmacokinetics metrics has been demonstrated in figure 2 This graph shows the time course of drug plasma concentrations over 96 hours following oral administrations every 24 hours. The AUC in steady state equals AUC_{∞} after the first dose administration.

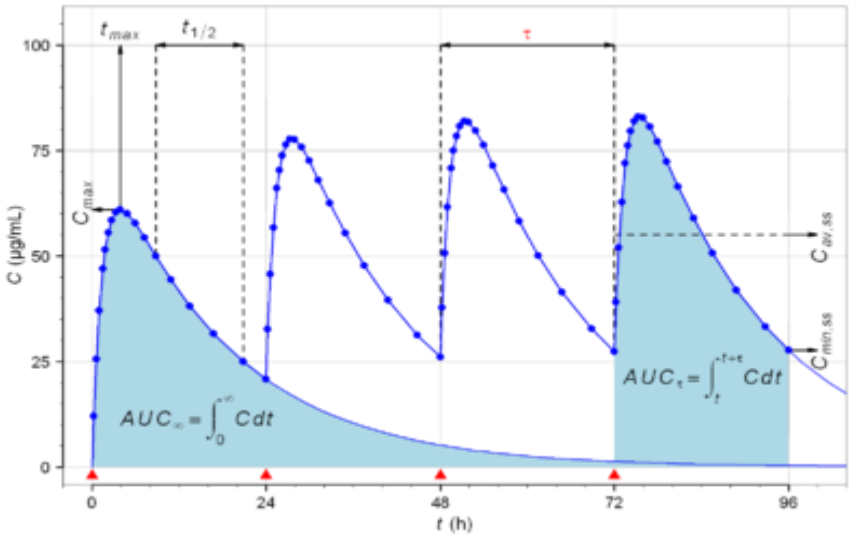

Figure 2: Showing graph of a model time course of drug plasma concentration that illustrates the main pharmacokinetics metrics. It shows the time course of drug plasma concentrations over 96 hours following oral administrations every 24 hours. The AUC in steady state equals AUC_{∞} after the first dose administration.[6]

Kinetic Compartmental Models - The Pharmacokinetic (PK) models

The PK modeling is performed by non-compartmental or compartmental methods. Non-compartmental methods estimate the exposure to a drug by estimating the area under the curve of a concentration-time graph. Compartmental methods estimate the concentration-time graph using kinetic models.[25] Non-compartmental methods are often more versatile in that they do not assume any specific compartmental model and produce accurate results also acceptable for bioequivalence studies.[3] The final outcome of the transformations that a drug undergoes in an organism and the rules that determine this fate depend on a number of interrelated factors. A series of functional models have been developed in order to simplify the study of pharmacokinetics. These models are based on a consideration of an organism as a number of related compartments. The simplest idea is to consider an organism as only one homogenous compartment. This **mono-compartimental model** assumes that blood plasma concentrations of the drug are a true reflection of the drug's concentration in other fluids or tissues and that the elimination of the drug is directly proportional to the drug's concentration in the organism (first order kinetics).[5,26] In multiple compartment models we can have model 1, model 11 and model 111 as indicated in figure 3.

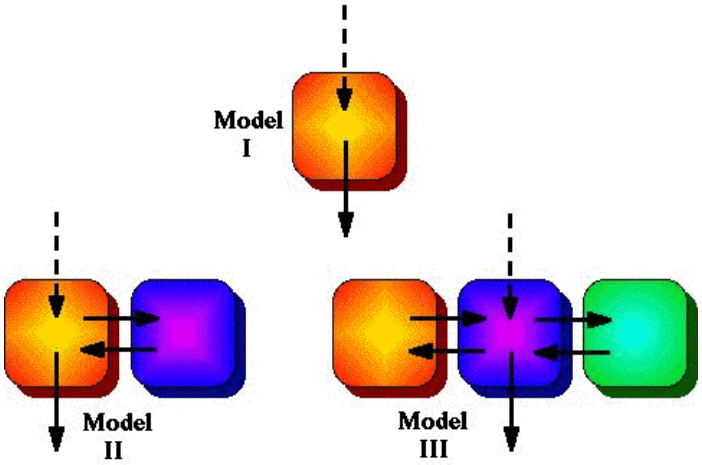

Figure 3: Graphic representation of One, Two and Three Compartment Models.[9]

The **two compartment model** will 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 happen 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.[8]

These models in some cases do not always truly reflect the real situation within an organism. For example is has been shown that, 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. 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 can be called 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 has been shown to occupy a variable position depending on a drug's ability to cross the barrier that separates the organ from the blood supply.[26]

This 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. In the real world each tissue will have its own distribution characteristics and none of them will be strictly linear. If we label the drug's volume of distribution within the organism $\mathbf{Vd_F}$ and its volume of distribution in a tissue $\mathbf{Vd_T}$ the former will be described by an equation that takes into account all the tissues that act in different ways, that is:

$$\mathbf{V_{dF}=Vd_{T1} + Vd_{T2} + Vd_{T3} + \ldots + Vd_{Tn}}$$

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 programmes have been developed to plot these equations [8]. However complicated and precise this 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 type of drug involved.[26]

Noncompartmental analysis

Noncompartmental PK analysis is highly dependent on estimation of total drug exposure. 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.[14]

Compartmental analysis

Compartmental PK analysis uses kinetic models to describe and predict the concentration-time curve. 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 some non-compartmental analyses is the ability to predict the concentration at any time. The disadvantage is the difficulty in developing and validating the proper model. Compartment-free modelling based on curve stripping does not suffer this limitation.[11] The simplest PK compartmental model is the one-compartmental PK model with IV bolus administration and first-order elimination. The most complex PK models (called PBPK models) rely on the use of physiological information to ease development and validation.

Single-compartment model

Linear pharmacokinetics is so-called because the graph of the relationship between the various factors involved (dose, blood plasma concentrations, elimination, etc.) gives a straight line or an approximation to one. For drugs to be effective they need to be able to move rapidly from blood plasma to other body fluids and tissues.[5]

The change in concentration over time can be expressed as $\mathbf{C_p = C_0 * e^{-ket}}$; where Cp is plasma concentration at time t, Co= initial concentration, Ke=elimination rate constant is time and time=time post dose.

Multicompartment model: 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 as shown in figure 4.

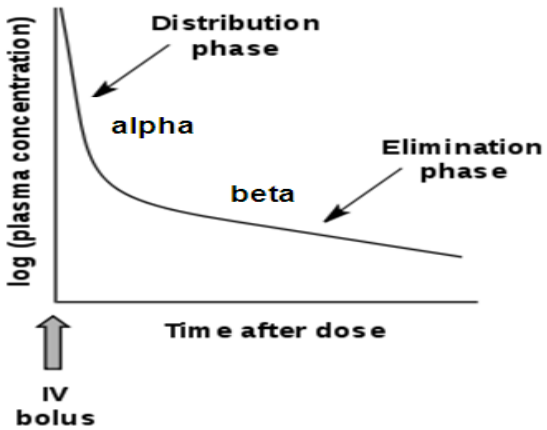

Figure 4: Plasma drug concentration vs time after an IV bolus dose.

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 pseudo-equilibrium of drug concentration is established between the central and peripheral compartments.[7]

Beta phase: A phase of gradual decrease in plasma concentration after the alpha phase. The decrease is primarily attributed to drug metabolism and excretion.[9] Additional phases (gamma, delta, etc.) are sometimes seen.[10]

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.[4] 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 metabolized 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.[16]

The kidneys can also establish active elimination mechanisms for some drugs, independent of plasma concentrations. It can therefore be seen that non-linearity can occur because of reasons that affect the whole of the pharmacokinetic sequence: absorption, distribution, metabolism and elimination.

Bioavailability

At a practical level, a drug's bioavailability can be defined as the proportion of the drug that reaches its site of action. From this perspective the intravenous administration of a drug provides the greatest possible bioavailability, and this method is considered to yield a bioavailability of 1 (or 100%). Bioavailability of other delivery methods is compared with that of intravenous injection («absolute bioavailability») or to a standard value related to other delivery methods in a particular study («relative bioavailability»).[21]

$$B_A = \frac{[ABC]_P . D_{IV}}{[ABC]_{IV} . D_P}$$

$$B_R = \frac{[ABC]_A . dose_B}{[ABC]_B . dose_A}$$

Once a drug's bioavailability has been established it is possible to calculate the changes that need to be made to its dosage in order to reach the required blood plasma levels. Bioavailability is therefore a mathematical factor for each individual drug that influences the administered dose. It is possible to calculate the amount of a drug in the blood plasma that has a real potential to bring about its effect using the formula:

De=B.Da

where *De* is the effective dose, *B* bioavailability and *Da* the administered dose. Therefore, if a drug has a bioavailability of 0.8 (or 80 %) and it is administered in a dose of 100 mg, the equation will demonstrate the following:

De = 0.8 x 100 mg = 80 mg

That is the 100 mg administered represents a blood plasma concentration of 80 mg that has the capacity to have a pharmaceutical effect.

Different forms of tablets, which will have different pharmacokinetic behaviours after their administration. This concept depends on a series of factors inherent to each drug, such as.[11]

Pharmaceutical form, Chemical form, route of administration, Stability and Metabolism.

These concepts, can be mathematically quantified and integrated to obtain an overall mathematical equation as follows:

De=Q.Da.B.

Where **Q** is the drug's purity.[11]

$$Va = \frac{Da.B.Q}{\tau}$$

where is the drug's rate of administration and is the rate at which the absorbed drug reaches the circulatory system.

By, using the Henderson-Hasselbalch equation, and knowing the drug's **pKa** (pH at which there is an equilibrium between its ionized and non-ionized molecules), it is possible to calculate the non-ionized concentration of the drug and therefore the concentration that will be subject to absorption:

pH= pKa +log B/A

When two drugs have the same bioavailability, they are said to be biological equivalents or bioequivalent. This concept of bioequivalence is important because it is currently used as a yardstick in the authorization of generic drugs in many countries.

Liberation of active substance from the delivery system (LADME)

A number of phases occur once the drug enters into contact with the organism, these are described using the acronym **LADME**[4]:

- **Liberation** of the active substance from the delivery system,
- **Absorption** of the active substance by the organism,
- **Distribution** through the blood plasma and different body tissues,
- **Metabolism** that is, inactivation of the xenobiotic substance, and finally
- **Excretion** or elimination of the substance or the products of its metabolism.

Some textbooks combine the first two phases as the drug is often administered in an active form, which means that there is no liberation phase. Others include a phase that combines distribution, metabolization and excretion into a «disposition phase». Other authors include the drug's toxicological aspect in what is known as ADME-Tox or ADMET.

Each of the phases is subject to physico-chemical interactions between a drug and an organism, which can be expressed mathematically. Pharmacokinetics is therefore based on mathematical equations that allow the prediction of a drug's behaviour and which place great emphasis on the relationships between drug plasma concentrations and the time elapsed since the drug's administration.[15]

Pharmacokinetics Analysis Mehods

- **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.[12,13]

- **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 insuring data integrity with such complex sample matrices. Much attention is paid to the linearity of the standard curve; however it is not uncommon to use curve fitting with more complex functions such as quadratics since the response of most mass spectrometers is less than linear across large concentration ranges.[14,15]

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.[17]

- **Population pharmacokinetics**

Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest.[18-20] Certain patient demographic, pathophysiological, and therapeutical features, such as body weight, excretory and metabolic functions, and the presence of other therapies, can regularly alter dose-concentration relationships. For example, steady-state concentrations of drugs eliminated mostly by the kidney are usually greater in patients suffering from renal failure than they are in patients with normal renal function receiving the same drug dosage. Population pharmacokinetics seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified. An advantage of population pharmacokinetic modelling is its ability to analyze sparse data sets (sometimes only one concentration measurement per patient is available).

Software packages used in population pharmacokinetics modelling include NONMEM, which was developed at the UCSF and newer packages which incorporate GUIs like Monolix as well as graphical model building tools; Phoenix NLME. Some medications have been studied that PK monitoring has been recommended as indicated in table 2, for antiepileptic drugs, cardioactive, immunosupressor, antibiotics and antiviral drugs.

Table 2: Medication for which Pk monitoring is recommended.

ANTIEPILEPTIC Drugs	CARDIOACTIVE Drugs	IMMUNOSUPPRESSOR Drug	ANTIBIOTIC Drugs	Antiviral (HIV) Drug
Primidone	Lidocaine	Tacrolimus	Amikacin	Efavirenz
Phenytoin	Digoxin	Sirolimus	Gentamicin	Ritonavir
Phenobarbital		Everolimus	Tobramycin	Tenofovir
Carbamazepine		Cyclosporine	Vancomycin	

Challenges of PK studies in herbal medicine within the Central African sub region

The use of herbs for treating various ailments dates back several centuries. Usually, herbal medicine has relied on tradition that may or may not be supported by empirical data. The belief that natural medicines are much safer than synthetic drugs has gained popularity in recent years and led to tremendous growth of phyto-pharmaceutical usage (Fokunang et al., 2011). Market driven information on natural products is widespread and has further fostered their use in daily life. In most countries in the sub-Saharan Africa there is no universal regulatory system that insures the safety and activity of phyto-pharmaceuticals. Evidence-based verification of the efficacy of herbal medicinal products (HMPs), botanicals) is still frequently lacking. However, in recent years, data on evaluation of the therapeutic and toxic activity of herbal medicinal products became available (Fokunang et al., 2011; Fokunang et al., 2017). The advances in analytical technology have led to discovery of many new active constituents and an ever-increasing list of putatively active constituents. Establishing the pharmacological basis for efficacy of HMPs is a constant challenge and of particular interest is the question of bioavailability to assess to what degree and how fast compounds are absorbed after administration of HMPs. Of further interest is the elucidation of metabolic pathways (yielding potentially new active compounds), and the assessment of elimination routes and their kinetics. These data become an important issue to link data from pharmacological assays and clinical effects.

Of interest currently is also the interaction of herbal medicinal products with synthetically derived drug products. A better understanding of the pharmacokinetics and bioavailability of phyto-pharmaceuticals can also help in designing rational dosage regimens. The relevance of this paper is to elucidate how pharmacokinetic and bioavailability studies can be relevant and conducted for some of the more important or widely used phytopharmaceuticals using the standard approach under regulatory compliance. Furthermore, address various drug interactions which show that caution should be exercised when combining phytopharmaceuticals with chemically derived active pharmaceutical ingredients.

The issue of herb-drug interactions has generated significant concern within the pharmaceutical industry and among regulatory authorities in recent years. Therefore, accurate models of predicting metabolic herb-drug interactions would be useful tools in efforts to avoid toxic adverse events. However, the majority of pharmacokinetic interactions listed for herbal medicinal products are based on theoretical predictions of the *in vitro* pharmacological effects of known constituents, which do not necessarily have to be the active ingredients. The prediction of herb-drug interactions is further complicated by the fact that pharmacokinetic data on active or (at least) known ingredients are often not available. It is therefore imperative for herbal research most especially within the Central African sub region where PK herbal studies is still at its infancy to address the potential of pharmacokinetic profiling for detecting herb-drug interactions, using the most frequently cited interactions in the literature as examples. In particular, common mechanisms of herb-drug interactions should be understood and knowledge on the available experimental methods for detecting such interactions, as well as the limitations of these models, The issue of whether the existing methods of detecting herb-drug interactions correlate with the clinical relevance. Effective screening tools that accurately predict metabolic herb-drug interactions would offer a tremendous advantage because it is not possible to study all potential herb-drug interactions in clinical trials.

Ethical Concerns with pharmacokinetics studies

The regulatory organs like the US food and drug administration (FDA) have set up regulatory guidelines for the production of clinical research for investigational drugs to be regulatory compliant. Other challenges imposed by Institutional and ethical review committees in adherence to the Helsinki declarations, the ethical fundamental principles for respect of humans in the conduct of clinical studies has raised awareness in the conduct of PK studies for the drug development process. The samples collected from the volunteers must respect the fundamental principles of participants consent, and the study ethically approved by a competent IRB or REC. The sample population must be statistically guided to reflect the normal distribution of event in a population. The laboratories for analysis of samples of volunteers must be GLP/GCP compliant; therefore the analytical laboratories must have accreditations by established recognized accreditation institutions. Within the Central African sub region PK studies for drug development are still at their infancy to support high throughput studies. There is lack of human resources and like of equipment. It is therefore important that if the developing nations need to emerge in the domain of drug development there is the need for capacity building, human resource strengthening and remobilization of revenue towards funding of PK research.

CONCLUSION

Clinical Pharmacokinetics plays an important role in the drug development process and gives a relationship between drug dosage regimens and the concentration time profiles. The three basic parameters that govern PK relationships are clearance, distribution elimination and half-life. The knowledge of distribution volume is relevant in estimating a loading dose in order to quickly attain a target concentration. On the other hand the knowledge of clearance can be useful in calculating the dose rate needed to retain a target concentration.

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