

Role of Pharmacokinetic Studies in Drug Discovery

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Abstract

Over the last few years, Pharmacokinetics has emerged as an integral part of drug development, especially when identifying a drug's biological properties. Understanding of pharmacokinetic and metabolism characteristic of the drug compounds is needed in designing appropriate human clinical trials. This document describes the basic principles of pharmacokinetic studies necessary for the submission of a new drug application and for re-examination of approved drugs.

Keywords: ADME; Cytochrome P450; Adverse events; Cmax; Noncompartmental and compartmental methods; ANOVA

Introduction

Pharmacokinetics provides a mathematical basis to assess the time course of drugs and their effects in the body. It enables the following processes to be quantified: Absorption, Distribution, Metabolism, and Excretion. These pharmacokinetic processes often referred to as ADME [1]; determine the drug concentration in the body when medicines are prescribed. A fundamental understanding of these parameters is required to design an appropriate drug regimen for a patient [2,3].

Absorption

Absorption is the process of a substance entering the blood circulation. Drug substances can enter the body via e.g. gastrointestinal tract, lung or skin, where they may be absorbed. The gastrointestinal tract is the most important of site of absorption, it is affected by several factors such as physicochemical parameters of the drug, gastrointestinal motility, drug concentration at the site of absorption.

Distribution

Distribution describes the reversible transfer of drug from one location to another location within the body. The distribution of a drug is influenced by factors such as lipid-solubility [4], concentration in plasma and in various tissues and binding to plasma proteins, transport proteins and tissues.

Metabolism

Metabolism is the process of irreversible transformation of parent compounds into daughter metabolites. The major site of metabolism in the body is the liver [5]. Metabolism in liver occurs in two stages: Phase I pathways in liver microsomes where the drug is functionalized and Phase II pathways in liver cells where the parent or the metabolite from Phase I gets conjugated. Phase I reactions in microsomes are catalyzed by a group of enzymes known as the cytochrome P450 system [6,7] that plays a significant role in drug metabolism. The common chemical reactions involved in Phase I are aromatic hydroxylation, aliphatic hydroxylation, oxidative N dealkylation, oxidative O-dealkylation, S-oxidation, reduction and hydrolysis. Most often this simple functionalization could be sufficient to make a drug more soluble, facilitating elimination through the kidneys. Further conjugation in Phase II [8] occurs by glucuronidation, sulfation, amino acid conjugation, acetylation, methylation or glutathione conjugation

to facilitate elimination. There are several factors that influence drug metabolism including route of administration, dose, genetics, disease state, and metabolic activity [9].

Excretion

Excretion is the process of eliminating the drug and other toxic substances from the body. Most of the drugs in the body are eliminated through the urine. Substances with low lipid solubility such as polar metabolites are excreted efficiently [10].

Pharmacokinetic Studies

Study design

The study should be designed in such a manner that the formulation effect can be distinguished from other effects. Typically [11,12] if two formulations are to be compared, a two-period, two-sequence crossover design is the design of choice with the two phases of treatment separated by an adequate washout period which should ideally be equal to or more than five half life's of the moieties to be measured. For single formulation studies a single-centre, single dose, randomized, open labeled, cross-over study is the design of choice [13-15].

Alternative study designs include the parallel design for very long half-life substances or the replicate design for substances with highly variable disposition.

The study was carried out in accordance with the principles of the Declaration of Helsinki and its amendments (World Medical Association, 2008) and the International Conference on Harmonization Guideline for Good Clinical Practice (59th WMA General Assembly, Seoul, October 2008) [16-18].

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Study population

The number of subjects required for a study should be statistically significant and it should be sufficient to allow for possible withdrawals or removals from the study.

Selection Criteria for Subjects

To minimize intra and inter individual variation subjects should be standardized as much as possible and acceptable. The studies should be normally performed on healthy adult volunteers with the aim to minimize variability and permit detection of differences between the study drugs. Subjects may be males or females; however the choice of gender should be consistent with usage and safety criteria.

The subjects were considered to be eligible if they satisfied the following inclusion criteria:

Male subjects in the range of 18 – 50 years of age and a body mass index between 19 and 28 kg/m² [19].

Subjects with normal findings as determined by a personal interview, a complete physical examination (blood pressure, pulse, weight, height, temperature, respiratory rate), and diagnostic testing that included a 12-lead electrocardiogram. Laboratory testing included a complete blood cell count, metabolic and hepatic tests, urinalysis [20], chest radiography, total protein, triglycerides, total cholesterol, platelet count, total and differential white cell counts, feces parasitological examination [21], pregnancy test for female subjects [22], and serologic tests for glucose, blood urea nitrogen, creatinine as well as syphilis, hepatitis B and HIV antibodies [23].

Willingness to follow the protocol requirement as evidenced by written informed consent was obtained from each subject participating in this study after adequate explanation of the aims, methods, objective, and potential hazards of the study [24].

Agreeing to, not using any medication (either prescribed, Over the counter or alternate medicines), including vitamins and minerals for 14 days prior to study and during the course of the study [25].

No history or presence of significant alcoholism or drug abuse in the past one year. Non-smokers, non tobacco chewer [26].

Subjects were excluded who met the following criteria:

History of acute or chronic illness, cardiovascular, renal, hepatic, ophthalmic, pulmonary, neurological, metabolic, psychiatric diseases or any malignancy.

Subjects were excluded if they had participated in any investigational trial within the previous 4 months; if they were hospitalized within 8 weeks before the beginning of the study [27].

Subjects were excluded if they were on any planned treatment during/until the study, including vitamins and mineral supplements [28].

History of a significant gastrointestinal condition that could potentially impair the absorption or disposition of the study medicine.

Refusal to abstain from smoking or consumption of tobacco products until last sample collection of each period.

Use of xanthine-containing beverages or food, and grape fruit juice for 48.00 hours prior to each drug dose.

Blood donation 90 days prior to the commencement of the study [29].

History of problem in swallowing tablets or capsules.

Known history of allergy to the study drug [30].

Candidates were excluded if laboratory values were significantly out of the reference range or if all tests had not been completed [31].

Study Conditions

Standardization of the study environment, diet, fluid intake, post-dosing postures, exercise, sampling schedules etc. is important in all studies.

Fasting and fed state considerations

Generally, a single dose study should be conducted after an overnight fast (at least 10 hours), with subsequent fast of 4 hours following dosing. For multiple dose fasting state studies, when an evening dose must be given, two hours of fasting before and after the dose is considered acceptable. No other food intake was permitted during the “in-house” period. Liquid consumption was permitted *ad libitum* six hours before and two hours after drug but caffeine and xanthine-containing drinks including tea, coffee, and cola were prohibited [32].

Sampling

There should be at least three sampling points during the absorption phase, three to four at the projected T_{max} , and four points during the elimination phase.

Venous blood samples for the determination of plasma drug concentrations were collected from an indwelling catheter or by direct venipuncture of an antecubital vein into tubes containing heparin or ethylenediamine tetraacetic acid (EDTA) as the anticoagulant [33,34].

Tolerability

Tolerability was assessed by monitoring vital signs (blood pressure, heart rate, body temperature) at baseline, 4.5, 11.5, and 23.5 hours, and at the end of each period, laboratory analysis results [35,36] and

The subjects were interviewed by the investigators during hospitalization and at the end of the clinical stage of the study concerning the occurrence adverse events (AEs) [37,38]. Subjects were asked to spontaneously report any AE to the investigators at any time during the study, including the washout period [39,40].

Bioanalytical Methods

The bioanalytical methods used to determine the drug and/or its metabolites in plasma [41], serum, blood or urine or any other suitable matrix must be well characterized, standardized, fully validated and documented to yield reliable results that can be satisfactorily interpreted.

Pharmacokinetics is often studied using mass spectrometry because of the complex nature of the matrix 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 [42,43] with a triple quadrupole mass spectrometer and HPLC [44,45]. Tandem mass spectrometry is usually employed for added specificity [46-48].

Pharmacokinetic Analysis

Pharmacokinetic analysis is performed by Noncompartmental or compartmental methods. Noncompartmental 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.

Analysis was done on parent drugs only not on metabolites [49]. The rate and extent of the absorption of the drug are primarily measured by plotting the plasma concentration-time profile [50], the time to reach the peak concentration (t_{max}) reflects the rate of absorption, while the peak concentration (C_{max}) reflects both the extent and the rate of absorption [51,52]. In order to have a true and accurate measurement of C_{max} , adequate number of sampling points should be placed at and around the anticipated C_{max} of the drug.

In a study conducted by *Fermin Valenzuela, Gabriela Davila et al.* [53], Noncompartmental pharmacokinetic analysis was performed using WinNonlin software, and the following pharmacokinetic parameters were calculated:

C_{max} : Maximum plasma concentration obtained graphically from the plasma concentration versus time profile

T_{max} : Time to reach C_{max} following drug administration, obtained graphically from the plasma concentration versus time profile [54].

AUC_{0-t} : Area under the plasma concentration-time curve from time 0 (administration) to time t (last sampling time) calculated through the trapezoidal method

AUC_{0-inf} : Area under the plasma concentration-time curve from time 0 (administration) extrapolated to infinity [55]

K_e : Terminal elimination rate constant

$t_{1/2}$: Elimination half-life, calculated as $0.693/K_e$ [56]

Statistical Analysis

The primary concern in pharmacokinetic studies is to limit the consumer's and manufacture's risk. This is done by using appropriate statistical methods for data analysis and adequate sample size [57]. In a study with a sufficient amount of data, mean values, variance, and confidence intervals of drug concentrations and pharmacokinetic parameters should be estimated using appropriate statistical methods [58-60]. Major variables such as drug concentrations and pharmacokinetic parameters should be analyzed based on their statistical properties of distribution, and data transformation such as logarithmic transformation should be performed whenever necessary. An analysis of variance (ANOVA) was used to determine the difference of the pharmacokinetic parameters, i.e. C_{max} , AUC_{0-last} and $AUC_{0-\infty}$ [61,62].

Conclusion

It is necessary to obtain human pharmacokinetic information for new drug development and to ensure the appropriate use of medicines. Clinical pharmacokinetic studies are performed to examine the absorption, distribution, metabolism, and excretion of an investigational drug or approved drug in healthy volunteers. Data obtained from such studies are useful for the design and conduct of

subsequent clinical trials. They are also necessary for appropriate analysis and evaluation of the efficacy and safety data obtained in clinical trials for new drug development and in post-marketing clinical trials. The results of clinical pharmacokinetic studies are useful for determining the appropriate use of medicines according to patient characteristics, such as disease and genotype of drug-metabolizing enzymes, and for predicting the influence of pharmacokinetic drug interactions and it also provide information for therapeutic drug monitoring (TDM).

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