Review Article

Basic Principles And Objectives Of Clinical Pharmacology Studies

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ARTICLE INFO	ABSTRACT

Clinical pharmacology studies are one of the most interesting clinical studies conducted during the clinical development of any new pharmaceutical product. Depending upon the pharmacological or therapeutic class of the product, it mainly involves different kinds of phase 1 studies. Clinical pharmacology studies are very specialized studies and are conducted with specific objectives to understand safety, tolerability, pharmacokinetics and / or pharmacodynamics of the drug. Not only designing of such studies, but conducting, analyzing and interpreting results of such studies are challenging. Designing such studies requires understanding of basic and clinical pharmacology as well as understanding of feasibility of conducting the studies. Conducting such studies requires knowledge and clinical skills. Bioanalytical knowledge and skills are required for bioanalysis in order to estimate the drug and / or metabolites of interest. For data analysis and interpretation; knowledge of pharmacokinetics, pharmacodynamics and biostatistics is required. Thus, such studies involve team of scientists from different disciplines including basic and clinical pharmacologists, clinicians, medical emergency experts, bioanalytical experts and statisticians. Results of such studies creates excellent base for phase 2 proof of concept studies. Some of these studies are also conducted in parallel or after phase 2 or phase 3 studies to address specific need. In this article, authors have summarized various clinical pharmacology studies with their basic principles and key objectives.

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INTRODUCTION:

Clinical pharmacology is the scientific discipline that deals with the relationship between drugs and humans. It includes development of new drugs, application of drugs as therapeutic agents, study the beneficial and adverse effects of drugs in individuals and society, and the deliberate misuse of drugs [1]. In pharmaceutical research, clinical pharmacology is a clinical development science which connects the laboratory research with the medical practice in order to bring promising drug therapies to the market. Clinical development process, if successfully identifies the potential and limitation of the new drug candidate; it can make the new drug a successful therapy. In the drug development process, on one side, the expectation is always for "GO" decision at each stage; but on other side, it is highly important to identify the limitations of the drug candidate so as to make earliest "NO-GO" decision. This is to ensure safety of the subjects and also to save time, money and efforts. Following are the two important considerations during clinical development of any pharmaceutical product.

- Avoid "False Positive" Decision…
- Not to Miss "True Negative" Decision…

Early phase clinical pharmacology studies are mainly proof of mechanism (POM) studies and are normally done within phase I clinical development program in healthy volunteers. These studies are designed to show that a new medicine reaches its target organ(s), interacts with its molecular target and affects the biology of the target as intended. POM studies greatly support the Proof of Concept (POC) studies (phase 2 clinical studies) and the POC studies support the Proof of Principle (POP) Studies (phase 3 clinical studies). That's why, early phase clinical development studies are one of the most important milestones of drug development process [2]. Phase 1 clinical studies are mainly early phase exploratory or clinical pharmacology studies conducted with following objectives [3].

- To find Maximum Tolerated Dose (MTD) in human
- To study adverse effects
- To study pharmacokinetics
- If possible, to study pharmacodynamics

Phase 1 clinical studies test "SAFETY" of investigational product (IP) for humans, hence, are also called "Initial Safety Studies". Series of studies are conducted, among 30 to 200 healthy volunteers or sometimes in patients (when the IP is not recommended to administer to healthy subjects)

mainly for anticancer cytotoxic products. Phase 1 clinical studies starts with first-in-human phase I clinical studies. Some of the phase 1 clinical studies are conducted after POC phase 2 studies e.g. Thorough QT/QTc studies, which requires therapeutic dose usually known after phase 2 or phase 3 studies. Following (but not limited to) are different clinical pharmacology studies conducted for new pharmaceutical product depending upon the pharmacological class.

- First-in-human (FIH) / First-in-man (FIM) Clinical Studies
- Single Ascending / Escalating Dose (SAD) and Multiple Ascending / Escalating Dose (MAD) Clinical Studies
- Cardiac Safety Studies / Thorough QT/QTc Studies
- Glucose Clamp Studies
- Skin Irritation and Sensitization Studies
- Human Skin Blanching (Vasoconstriction) Assay
- HPA Axis Suppression Effect Studies
- Pharmacokinetics (PK)-Pharmacodynamics (PD) Studies
- Dose-Response / Concentration-Response Studies
- PK Studies for Inhaled or Nasal Spray Products for Gastro-intestinal Tract (GIT) Absorption
- Pharmacokinetic / Absorption Distribution Metabolism Excretion (ADME) Studies
- Drug Genotype Interaction Studies
- Food Effect Studies
- Gender Effect Studies
- Chronokinetics Chronodynamics Studies
- Age Effect Studies
- Drug Drug Interaction (DDI) Studies
- Bioavailability (BA) Studies
- Bioequivalence (BE) Studies

First-in-human (FIH) / First-in-man (FIM) Clinical Studies

FIH clinical studies are part of the exploratory phase of drug development and represent a significant milestone in the clinical development of new medicines (Fig 1). At this stage, only pre-clinical data are available to guide dose selection, population, study design, safety monitoring and appropriate expertise, and all of these are critical to maximise the safety of the study subjects and the quality of the data. The available information may be in a form of one or more of the following.
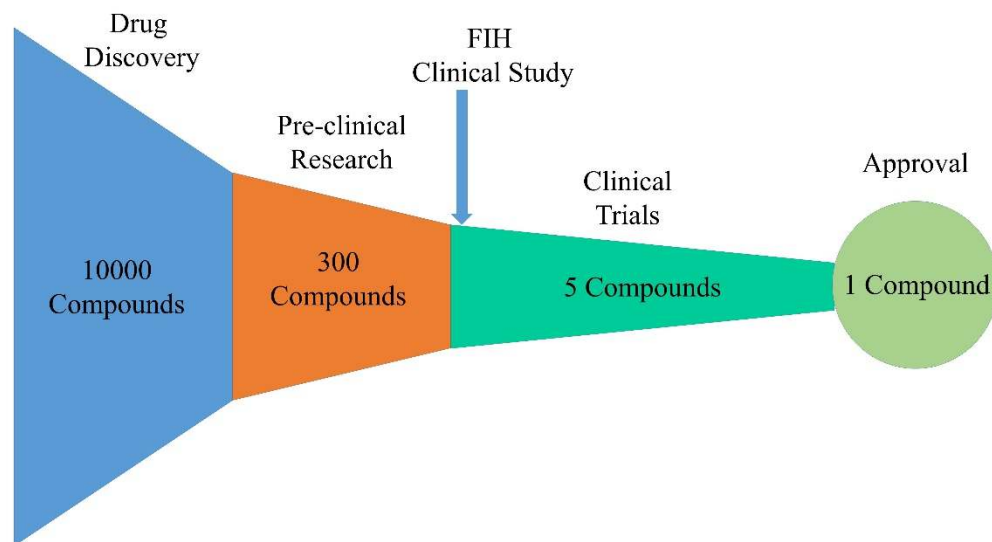
Fig 1: First-in-human Clinical Study in Drug Development Pathway

- No Observed Effect Level (NOEL): It is the highest dose tested in an animal species with no detected effects (including all kinds of pharmacological effects).
- No Observed Adverse Effect Level (NOAEL): It is the highest dose tested in an animal species that does not produce a significant increase in adverse effects in comparison to the control group. Adverse effects that are biologically significant, even if not statistically significant, should be considered in determining an NOAEL.
- Lowest Observed Adverse Effect Level (LOAEL): The lowest dose tested in an animal species which has found with adverse effect.
- For a given drug, NOEL < NOAEL < LOAEL.
- Pharmacologically Active Dose (PAD): It is the lowest dose tested in animals which produced intended pharmacological activity.
- Maximum Recommended Starting Dose (MRSD): It is the highest dose recommended as the initial dose in a clinical study. In clinical studies of adult healthy volunteers, the MRSD is predicted to cause no adverse reactions. The units of the dose (e.g., mg/kg or mg/m2) may vary depending on practices employed in the area being investigated.
- Highest Non-Severely Toxic Dose (HNSTD): The highest dose level that does not produce evidence of lethality, life-threatening toxicities or irreversible findings. Mainly for anticancer products, HNSTD is used to for FIH study.

Based on these pre-clinical data derived information, the FIH studies are designed and conducted. FIH studies are generally conducted in men, hence, sometimes FIH studies are also known as FIM Studies.

Single Ascending / Escalating Dose (SAD) and Multiple Ascending / Escalating Dose (MAD) Clinical Studies
FIH Studies in which the new compound is first studied in cohorts of healthy volunteers or patients with single increasing dose are called SAD studies. The objectives of SAD studies are to study safety, tolerability and pharmacokinetic of the investigational product administered in single dose (Fig 2).
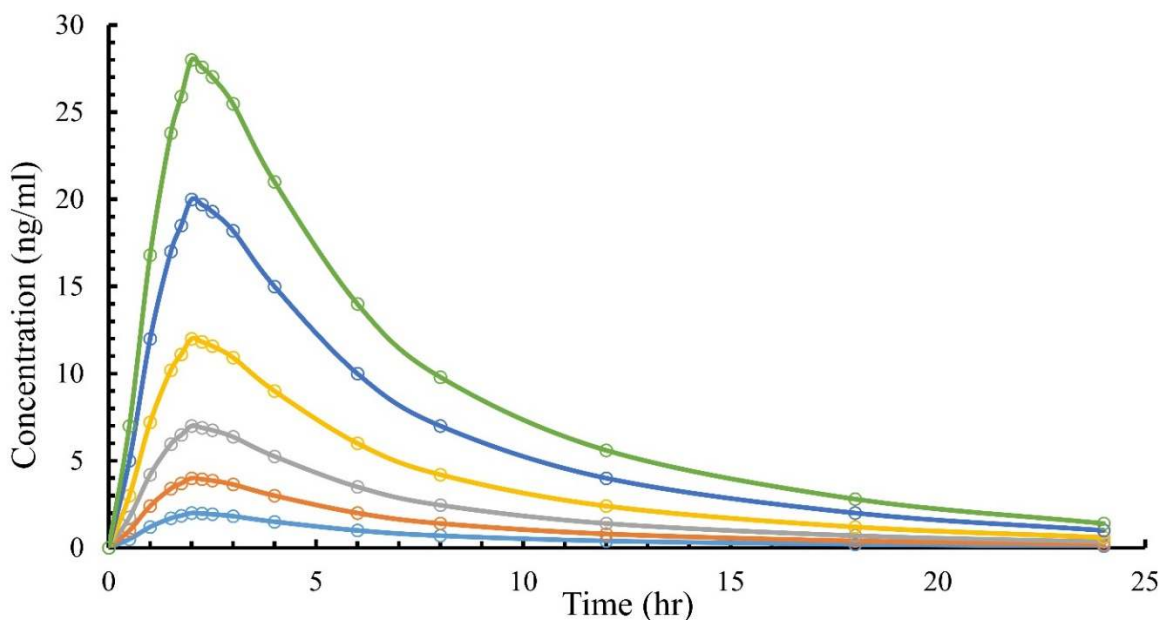
Fig 2: Typical Pharmacokinetic Chart in Single Ascending / Escalating Dose Study

Studies in which the new compound is administered in cohorts of healthy volunteers or patients in multiple administrations with increasing multiple dose are called MAD studies. The objectives of MAD studies are to study safety, tolerability and pharmacokinetic of the investigational product administered in multiple doses (Fig 3).
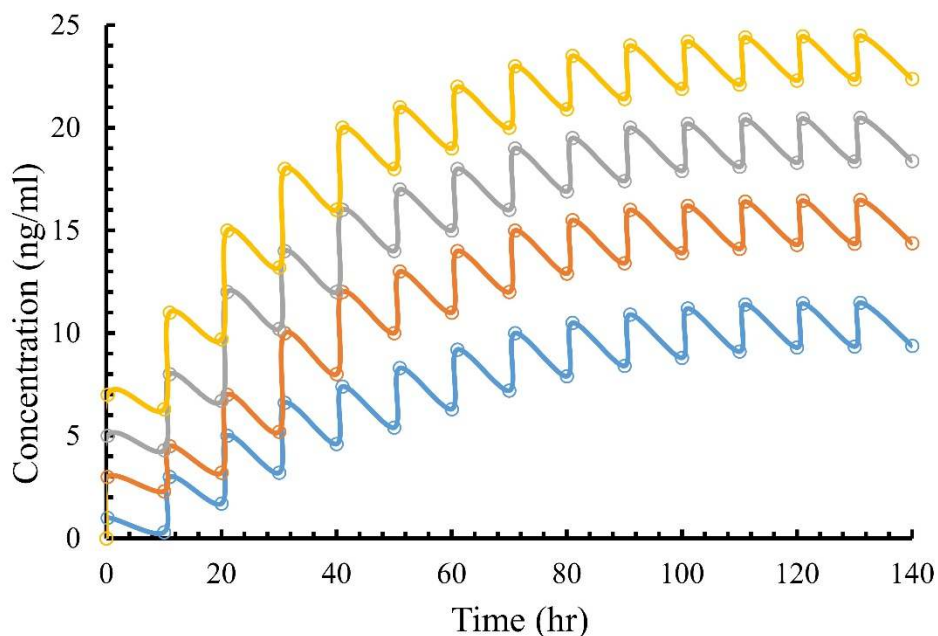

Fig 3: Typical Pharmacokinetic Chart in Multiple Ascending / Escalating Dose Study

Objectives of such dose escalation studies is to find maximum tolerated dose (MTD), to check tolerability upto certain dose and / or to find the recommended phase 2 dose (RP2D). These studies are conducted in cohorts of subjects with dose to be administered in escalated manner. There are various designs available for such dose escalation studies, 3 + 3 design is the most commonly used study designs for such studies [4]. The dose is escalated till MTD or to a certain pre-defined limit and dose escalation is carried out based on number of subjects reported with dose limiting toxicities

(DLTs). Most commonly used definition of DLTs in healthy subject based SAD and MAD studies is: "Adverse events (AEs) that are presumably related to the investigational product and are considered unacceptable (because of their severity and/or irreversibility) that limit further dose escalation or continuation of existing dose administration" [5]. Many-times SAD or MAD study is conducted in patients (especially when the investigational product is not recommended to be administered to healthy subject for clinical study e.g. cytotoxic anti-cancer drugs). In cancer patient based dose escalation study, Common Terminology Criteria (CTC) for Adverse Events based definition of DLT is commonly used. CTC based DLT is defined as "CTC grade 4 hematological toxicity or any grade 3 or grade 4 non-hematological toxicity with the exception of alopecia, inadequately treated grade 3 or 4 nausea and vomiting or isolated laboratory change without any clinical significance". Dose escalation decision is made based on complete safety evaluation and is documented in a form of report. Dose escalation rule is pre-defined and as per the rule, the subjects for next cohort is enrolled and treated with the higher dose [6].

The above discussed SAD MAD study designs are called rule based designs. Model based study designs are also used specially to improve precision in estimating the RP2D as well as efficiency during dose escalation. Model based designs establishes dose-toxicity curve prior to patient enrolment and uses toxicity data from enrolled patients to modify curve as study proceeds. Continual reassessment method (CRM) and its modifications, time to event CRM, escalation with overdose control, modified toxicity probability interval, fractional dose-finding methods and mixed-effect proportional odds model are various model based designs for dose escalation studies [4].

Cardiac Safety Studies / Thorough QT/QTc Studies
Some non-antiarrhythmic drugs (e.g. Astemizole, Moxifloxacin, Quinine, Chloroquine etc.) have found to delay cardiac repolarization, an effect that can be measured as prolongation of the QT interval on the surface electrocardiogram (ECG). It is well known that delay in cardiac repolarization creates an electrophysiological environment that favours the development of cardiac arrhythmias, most clearly torsade de pointes (TdP) and possibly other ventricular tachyarrhythmias as well [7]. Many drugs (e.g. Cisapride, Clobutinol, Dofetilide, Grepafloxacin, Sparfloxacin, Terfenadine, Terodiline) have been banned or withdrawn from one or more than one country market because of one of the reason as QT prolongation.

Regulatory bodies many-times recommends to provide clinical studies data assessing the potential of a drug to delay cardiac repolarization. This is mainly required for drug or members of chemical or pharmacological class that have been found to be associated with QT/QTc interval prolongation, TdP, or sudden cardiac death during post-marketing surveillance or is suspected QT prolonging investigational new drugs. This assessment can be done by conducting a dedicated study called Thorough QT/QTc Study. The 'thorough QT/QTc study' is intended to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation [8]. The thousands of ECGs are captured at high frequency (e.g. 1000Hz) and different ECG intervals including QT interval are measured on digital ECGs using digital callipers in software system in compliance with 21 Code of Federal Regulation (CFR) part 11 [9]. The threshold level of regulatory concern is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms. A negative 'thorough QT/QTc study' is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms [8]. When the largest time-matched difference exceeds the threshold, the study is termed 'positive'. The positive control should have an effect on the mean QT/QTc interval of about 5 ms. Detecting the positive control's effect will establish the ability of the study to detect such an effect of the study drug. Absence of a positive control should be justified and alternative methods to establish assay sensitivity provided [8].

Glucose Clamp Studies
The glucose clamp studies are carried out for Insulin and other glucose lowering investigational drugs. These studies are carried out by measuring glucose-lowering effect of the investigational product by means of a variable glucose infusion rate (GIR), so that blood glucose concentrations are maintained or "clamped" at a predefined target level. GIR is used as a surrogate marker for the pharmacodynamic effect of the investigational product. In hyperglycemic clamp, glucose level in plasma is raised acutely to a fixed hyperglycemic plateau and maintained for 2 h. This is achieved by an intravenous glucose infusion consisting of two phases: first 15-min priming dose followed by maintenance dose that is computed at 5-min intervals. The hyperglycemic clamp is used for assessment of insulin secretion effect (quantification of beta-cell sensitivity to glucose) [10,11]. In hyperinsulinemic euglycemic clamp, the plasma insulin concentration is raised acutely to a plateau

and maintained. In the published studies, the plasma insulin concentration was raised to approximately 100 µU/ml above basal and maintained at this level for 120 min. This will result in rapidly developing hypoglycaemia hence, this clamp also involves glucose infusion at required variable level to maintain euglycemic level with the insulin infusion of predetermined fixed dosage. The hyperinsulinemic euglycemic clamp is used for the assessment of insulin sensitivity [10,11].

Skin Irritation and Sensitization Studies

Transdermal products may have properties to cause skin irritation and / or sensitization. It may be the effect of the delivery system, or the system in conjunction with the drug substance. In the development of transdermal products, dermatologic adverse events are evaluated primarily with animal studies and general safety evaluations in the context of large clinical studies. However, separate skin irritation and skin sensitization studies are also used for this purpose. These are designed to detect irritation and sensitization under conditions of maximal stress. In skin irritation studies, the patch is applied for 23 hrs for about 21 days daily; and scoring of skin reactions and patch adherence are carried out by a trained and blinded observer at each patch removal. Skin sensitization studies involves induction phase, rest phase and challenge phase. During induction phase, patch is applied at same site for about 3 times weekly for 3 weeks. The rest phase follows induction phase and it involves no patch application for about 2 weeks. Then in the challenge phase, the patch is applied to the new site for about 48 hrs and skin reactions are evaluated by a trained blinded observer for up to 72 hrs after patch removal [12].

Human Skin Blanching (Vasoconstriction) Assay

The human skin blanching (vasoconstriction) assay is mainly used for the assessment of topical corticosteroids. It uses the skin pallor induced at the site of application as an indicator of the potency of the drug or efficacy of the delivery vehicle [13]. This human skin blanching assay is also used in in-vivo bioequivalence assessment of generic formulation.

HPA Axis Suppression Effect Studies

Hypothalamic-pituitary-adrenal (HPA) axis suppression resulting in reduced cortisol response may cause an impaired stress response and an inadequate host defence against infection. This remain a cause of morbidity and mortality especially when it is induced by drugs requiring long term use. Glucocorticoids are widely used for many clinical indications for long time and are known to cause HPA axis suppression. HPA axis suppression effect studies are carried out to study the effect of multiple doses of investigational product on of HPA axis [14]. The 24 hr cortisol profiling of all subjects is carried out at baseline as well as post treatment and compared for the effect on HPA axis. Uniform diet and sleep pattern with control over stress inducing factors are ensured in order to reduce variability in the results.

PK-PD Studies

PK-PD correlation is always one of the important methods of studying the effect of drug. PK-PD analyses is done as part of a Phase I or Phase II study. A well-designed PK-PD study yields more precise values of the basic PK parameters (C-max, T-max, AUC etc.) as well as more sophisticated PK parameters, such as the actual rates of absorption and elimination, drug distribution in various body compartments and the rates of creation and elimination of drug metabolites. A PK-PD study also acquires many other PD measurements that indicate the drug's effects on the body, often at the same (or nearly the same) sampling time points as for the PK samples. PK-PD study given data have been found to be greatly useful in clinical development of new drugs [15-19].

Dose-Response / Concentration-Response Studies

Knowledge of the relationships among dose, drug-concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. Dose-response studies are useful in assessing drug tolerance and safety, and invaluable in Phase II for characterizing drug efficacy [20]. These are also one type of PK-PD studies. Conducting dose-response studies at an early stage of clinical development may reduce the number of failed phase 3 studies, speeding the drug development process and conserving development resources [21]. Prospective randomized concentration-response studies are critical to defining concentration monitoring therapeutic windows. They are also useful when pharmacokinetic variability among patients is great. In that case, a concentration response relationship may in principle be discerned in a prospective study with a smaller number of subjects than could be the dose response relationship in a standard dose-response study. A number of specific study designs are being used to assess dose-response e.g. parallel dose-response, cross-over dose-response, forced titration and optional titration (placebo-controlled titration to end-point) [21].

PK Studies for Inhaled or Nasal Spray Products for GIT Absorption

Inhaled drug products includes dry powder inhaler (DPI), metered-dose inhaler (MDI), nebulizers and nasal spray products. Unlike the traditional dosage forms, most inhalation and nasal spray products are designed as locally acting in the lungs or nasal mucosa, and their drug delivery does not solely or necessarily directly rely on the systemic circulation. For such products, there is always a possibility of enteral absorption of the proportion of inhaled drug which may have be swallowed and have contributed to the systemic concentration through GIT absorption. Hence, a study may be carried out for new drugs to study GIT absorption of investigational product administered using inhaled or nasal spray delivery system. This can be studied by inhibiting the GIT absorption of orally administered component of the dose and analysing the systemic exposure which represent only the absorbed component from respiratory track. Administering charcoal suspension at various intervals may eliminates the enteral absorption of the swallowed proportion and the systemic concentration reflects only that fraction of the drug that has been absorbed form the respiratory tract [22,23].

Pharmacokinetic / ADME Studies

ADME is an abbreviation in pharmacology for "absorption, distribution, metabolism, and excretion". Various studies carried out to study absorption, distribution, metabolism, and excretion of the investigational product are called human ADME studies. These are one type of PK studies especially carried out during early phase of clinical development. Some ADME studies are conducted in very early stage of drug development and involves use of micro-dose and radio labelling of the substance. Such studies are known as phase 0 or micro-dose clinical studies [24].

Clinical Pharmacogenomic Studies / Drug Genotype Interaction Studies

Thorough understanding of the different cytochrome P450 isoenzymes and drug transporters have increased the requirements to study the impact of pharmacogenetic polymorphisms on drug pharmacokinetics and interactions. Regulatory requirements have been evolved for industry to classify cytochrome inhibitors and inducers, test the effect of drug interactions in the presence of polymorphic enzymes, and evaluate multiple potentially interacting drugs simultaneously [25]. Clinical Pharmacogenomic (PGx) studies are conducted to study the effects of these genomic differences. Clinical PGx studies provide information on exposure in genomically defined subgroups and depending on an understanding of the PD consequences of blood levels (e.g. concentration / response relationships), this information could influence dosing in later randomized controlled trials or during therapeutic use of the product [26]. Clinical PGx studies focused on PK are usually performed in phase 1 clinical development stage using healthy volunteers, with additional attention to the effects of gender, age, and race / ethnicity. Clinical PGx study are conducted at relevant clinical doses. A lower dose or different titration interval are used in subjects with certain genotypes that could cause high and unsafe exposure or excessive pharmacological response to the drug. Interpretation of findings in a clinical PGx study, such as changes in exposure in specific genotypes, are aided by a good understanding of dose / concentration response relationships for both desirable and undesirable drug effects in the general population and in subpopulations with different genetic variations [26]. Usually, PK measurements and parameters are used for consideration of genotypic effects. Biomarkers of drug response related to a drug's intended pharmacological effect, suspected off-target effects, and / or safety, when available, are also incorporated into clinical PGx studies to measure whether or not genetic factors influencing exposure or target response will have an impact on clinical outcomes [26].

Food Effect Studies

Food can change the bioavailability of a drug and can influence the PK of the products. Food effects on bioavailability can have clinically significant consequences. Food can alter PK of drug by various means, including

- Delaying gastric emptying
- Stimulating bile flow
- Changing GIT pH
- Increasing splanchnic blood flow
- Changing luminal metabolism of a drug substance
- Physically or chemically interacting with a dosage form or a drug substance.

Food effect bioavailability studies are usually conducted for new drugs and drug products during the investigational new drug period to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions. Fed bioequivalence studies, on the other hand, are conducted for generic drug application to demonstrate their bioequivalence to the reference product under fed conditions [27].

Sex / Gender Effect Studies

Sex is the property or quality by which organisms are classified as male or female on the basis of their reproductive organ anatomy and physiology, while gender is expressed in terms of masculinity and femininity [28]. However, in this article, we consider sex and gender similar as per above definition of sex only, as we are not discussing here in context with difference between masculinity and femininity. Some of the factors that influence the effect of a medicine may be important when considering potential differences in response between men and women. Sex specific influences can also play a significant role in the effect of the drug. Such variation in drug effects may arise from a variety of sources. e.g. difference in endogenous and exogenous hormones, difference in habits such as smoking or alcohol use. For example, differences in drug absorption (rifampicin, benzylamine and IM cephradine) between males and females [28], higher apparent cytochrome P450 3A4 activity in women than in men [29]. Hence, it is important to identify to the maximum extent possible, the effect of gender on PK or PD of drugs among individuals. Evaluation for such effect is generally conducted by subpopulation analyses in the clinical studies; however, sometimes, formal PK or any other clinical studies may be conducted for the same, such studies are known as Sex / Gender Effect Studies.

Chronokinetics Chronodynamics Studies

Although PK and PD are generally assumed to be time invariant, some investigational products have been reported to exhibit time-varying PK or PD. For example, propranolol has been reported to show higher C-max and an earlier T-max after the morning dose than after the evening dose [30,31]. Heparin has been reported to exhibit higher anticoagulant effects at night than in the morning [31]. Cilostazol PK shows intraday and interseasonal variation [31]. Such phenomena are known as chronokinetics and chronodynamics. Chronokinetics is variations in absorption, distribution, metabolism, or excretion and chronodynamics is variations in drug effects or adverse drug reactions at different time. Studies conducted to study such phenomena are known as chronokinetics and chromodynamics studies. Some of these studies are also called Time Effect Studies / AM-PM Studies or Season Effect Studies.

Age Effect Studies

Ageing is the progressive accumulation of more or less random changes which reduces homeostatic ability and lowers the ability to cope with external stresses. The reduced homeostatic ability affects different systems in different subjects, thus explaining at least partly the increased inter individual variability occurring as people get older [32]. Physiological and disease induced changes with aging might affect PK and / or PD of many drugs [33]. PK changes include a reduction in renal [34] and hepatic clearance and an increase in volume of distribution of lipid soluble drugs (hence prolongation of elimination half-life) whereas PD changes involve altered (usually increased) sensitivity to several classes of drugs such as anticoagulants, cardiovascular and psychotropic drugs [32]. The studies conducted to study all these effects of aging are called Age Effect Studies.

Drug Drug Interaction (DDI) Studies

Clinical DDI studies compare substrate concentrations in the absence and presence of a perpetrator drug in vivo. Clinical DDIs are evaluated in prospective studies and / or retrospective evaluations. Proper and thorough DDI evaluations that can make regulatory decision-making require specifically designed studies. Index perpetrators predictably inhibit or induce drug metabolism or transport by a given pathway and are commonly used in prospective DDI studies. Index substrates have defined changes in systemic exposure when administered with a strong inhibitor or inducer for a specific drug elimination pathway. Index substrates and perpetrators are not chosen based on their use in the investigational drug's target population, but rather because of their well-defined interaction effects that provide information about the DDI potential of the investigational drug. The purpose of most DDI studies is to determine the ratio of a measure of substrate drug exposure (e.g. AUC ratio) in the presence and absence of a perpetrator drug [35].

Bioavailability (BA) Studies

Bioavailability refers to the relative amount of drug from an administered dosage form which enters the systemic circulation and the rate at which the drug appears in the systemic circulation. Absolute bioavailability is the percentage of the administered dose which reaches the systemic circulation. Its estimation involves comparing drug exposure following administration of the test dosage form with that of an intravenous administration, assumed to be 100% available. Relative bioavailability involves comparison of two formulations (or two routes of administration of the same formulation) [36,37]. BA studies are carried out to find bioavailability of the active ingredient or active moiety in the pharmaceutical formulation.

Bioequivalence (BE) Studies

Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Because the rate and extend to which the active ingredient is available at site of action is considered similar in bioequivalent products; it is accepted that the product will have similar pharmacological effects and hence similar therapeutic effects. This concept of bioequivalence has been adopted by the pharmaceutical industry and national regulatory authorities throughout the world for over 30 years [38] and based on it, many generic products have been approved. For such generic drugs, the PK studies conducted to prove bioequivalence of test product with reference product is known as bioequivalence studies. In bioequivalence studies, the PK profile of a test drug product is compared to that of a reference drug product. Such studies are also carried out to establish bioequivalence between two products for certain formulation or manufacturing changes occurring during the drug development and post-approval stages.

CONCLUSION

Clinical pharmacology studies are the most important studies contributing to the prescribing information of the pharmaceutical product. For drug discovery, artificial intelligence-based technologies can help to improve the outcome of drug discovery and also to replace some of the procedures of drug discovery [39]; but for clinical development, no alternative technologies have yet been identified which could replace clinical studies to greater extent. Although some simulation technologies are available to optimize clinical trial design and to some extend predicting some of the data [40-43], there are no alternatives of clinical pharmacology studies available. Considering importance of clinical pharmacology studies in drug development, this article will be helpful to the readers to understand objectives and principles of above discussed clinical pharmacology studies.

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