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REVIEW ARTICLE

POPULATION PHARMACOKINETICS

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ABSTRACT

The current interest in population pharmacokinetics stems from the concern that the pharmacokinetics of new drugs are not studied in relevant populations, that is, patients likely to receive the drug at an early enough stage in the drug's development. The obvious time to collect pharmacokinetic information on the target population is during large-scale clinical trials carried out during phase III and post marketing surveillance of the drug development programme. Population pharmacokinetics has emerged as a key role in clinical pharmacology to study drug use by designing rational dosage forms and dosage regimes. Quantitative representation of the dose-concentration-response relationship should provide information for prediction of the level of response to a certain level of drug dose. Several mathematical approaches describe the dose-concentration-response relationships. Depending on the single dose or the steady-state measurements carried out, clinical significance of estimated parameters will be valuable when underlying physiologic processes (disease, age, gender, etc.) are considered. The purpose of this review article is to describe the significance of population pharmacokinetics i.e. variability of drug disposition between individuals.

KEY WORDS

Population Pharmacokinetic; Intersubject variability

INTRODUCTION

Pharmacokinetic studies are carried out to understand the disposition of drugs (either endogenous or exogenous in nature) in humans to study the inferences underlying in the behavior of the system by repeated measurements in various individuals or population, with the objective of computing the overall response to a drug[7].

Population pharmacokinetic analysis and other research would not greatly benefit the pharmaceutical industry; but it became a significant tool for further drug development process[16]. Knowledge of population pharmacokinetic can assist one to choose initial drug dosage, to modify dosage aptly in response to observed drug levels, to make rational decision on therapy[11].

"Population pharmacokinetics can be defined as a study of the basic features of drug disposition in a population, accounting for the influence of diverse pathophysiological factors on the pharmacokinetics and explicitly estimating the magnitude of the interindividual and intraindividual variability". The estimation

of these variance components is one of the major aims of a population study.

Population pharmacokinetics is the study of the variability in plasma drug concentrations between individuals when standard dosage regimens are administered. Certain patient demographical, pathophysiological, and therapeutical features, such as body weight, excretory and metabolic functions, and the presence of other therapies, can regularly alter dose-concentration relationships. Population pharmacokinetics is an area of clinical pharmacology that aims at quantitative assessment of pharmacokinetic parameters, and the between-individual and residual variability in drug absorption, distribution, metabolism, and excretion[4].

Pharmacokinetic variability is due to several factors such as

1. Demographic factors mainly include gender, body weight or surface area, age, and race[12, 13].
2. Environmental factors mainly being smoking, diet, and exposure to pollutants.
3. Genetic phenotype can also affect clearance of drugs via hepatic metabolism by polymorphic cytochrome P450 isoforms (eg, CYP2D6, 2C19, 2C9, 2A6).
4. Drug-drug interactions also come into play.
5. Physiologic conditions like pregnancy and disease states like renal and hepatic impairment can also affect the drug response
6. Additional factors like circadian rhythm, also the timing of meals, activity and posture can have effect on the drug response.

Briefly, certain pathophysiological condition of patients can regularly be shown to alter the dose-concentration relationship. For drugs eliminated largely by the kidney, renal failure usually causes steady-state drug levels to be greater than those of normal patients receiving the same drug dosage. For e.g. Diazoxide, Digoxin, Furosemide, Gentamicin, Phenobarbital, Tetracycline etc are the list of drugs which requires dose alteration depending the renal function. The influence on the elimination half life, which provide idea of dosing interval and volume of distribution which allows choice of loading dose, are of secondary interest. Pathophysiologic effects on pharmacokinetic are studied before a drug is marketed, so that appropriate dosage adjustments can be made for population subgroups with altered pharmacokinetics[6].

The population pharmacokinetics is the degree of interindividual kinetic variability that has been found difficult to correlate with measurable pathophysiological factors. The inherent variability in drug disposition is known as inter-subject pharmacokinetic variation. For a group of subjects given a fixed dose of a single drug, a large variation in serum drug levels (i.e. a coefficient of variation of 60% or greater) is commonly noted[18]. Source of variation that contributes difference between expectation and outcome are usually categorized as interindividual and residual in nature. Although expected parameter values can be calculated for an individual patient based on previous research and experience, the parameter values of a particular patient will differ from the expected values because of interindividual variability. An example is the degree of variability in clearance values remains different from patient to patient after the influences of age, weight, renal function, and other known factors have been taken into account. The magnitude of such variability is important for several reasons. First, the safety and efficacy of a drug decreases as inexplicable variability increases. Because of the extensive inter-subject variation in plasma concentrations and resultant therapeutic effects, the appropriate dosage of drugs with high inter subject variability has to be defined in individual patients. This procedure would be expected to result in a reliable treatment regime for individual patients. Sometimes the variability can be eliminated, for example, if it is due to large variability in F (F is bioavailability) traceable to a defect in manufacture[6].

Population pharmacokinetic analysis provides opportunity to estimate variability in the drug response and also helps to identify the exact source of this variability. Variability in the drug response is termed as fixed and random effects. The population average values of pharmacokinetic parameters are considered as fixed effects. Fixed effects include demographic, physiological and biochemical data such as age, weight, sex, renal function, enzyme levels[9]. Fixed-effect parameters measure central tendency, or typical relationships between concomitant factors and individual kinetic parameters, interindividual random-effect parameters measure variability in perhaps several aspects of kinetics, and intraindividual random-effect parameters measure total intraindividual kinetic variability and measurement error[11].

The estimation of fixed and random parameters is found to be useful for developing dosing guidelines and for revising dosing regimens in specific patient population[19]. The measurement of population pharmacokinetic related parameters are found to be useful in the estimation of covariate effects, the exploration of concentration/effect relationships and the design of prior dosing regimens[9].

Population pharmacokinetics studies carried out in the mixed population that is sampled sparsely allows data to combine from varying sources[8]. For example, one could pool data from several different trials, study centers, variable biometrics, intense plus sparsely sampled populations, or experimental plus observational data. The combining of different data sets often increases power to identify multi-compartment or nonlinear models, incorporate additional covariates, or gain precision in the estimation of the model.

A population pharmacokinetics data analysis should include relevant covariates[10], e.g. age, weight, gender, creatinine clearance, co-medication, and concomitant diseases. Quantitative relationships between covariates and pharmacokinetic parameters often help to predict individual pharmacokinetic. The knowledge of the relationship between dose, concentration, response, and pathophysiology is also essential for designing dosing strategies for rational therapeutics that may not necessarily require therapeutic drug monitoring[4].

Study Design of Population Pharmacokinetics

The study designs for population pharmacokinetic are considerably more complex than single individual studies. Contemplation must be given to the dosing schedule, the number of elementary designs, the composition of each elementary design and the proportion of patients allocated to the design. In addition, the cost of the study and the constraints required by the sponsor must be integrated into the process to yield a practical design[17]. When the problem has been confirmed, an appropriate study design needed to address the problem[3].

While carrying out population pharmacokinetics study baseline pharmacokinetics parameter, models and drugs major elimination pathways in humans should be known. The amount of information collected from these population pharmacokinetics studies depends on the study design and data available. With this information's population pharmacokinetic studies can be classified into three groups (a) single sampling design (b) multiple sampling design and (c) full pharmacokinetic sampling design[4, 20].

In single sampling design where one blood sample is obtained from each patient at or close to the trough of drug concentrations. Measuring peak plasma concentration is not advised. Frequency distribution of plasma or serum drug levels indicates the variability of drug concentration which will indicate the variability of the drug trough concentration. Covariates are regressed against these results. Components of variability i.e. interindividual and residual variability cannot be separated. This method will identify, qualitatively, not quantitative, pharmacokinetically relevant covariates and their differences among

subpopulations. Pharmacokinetic information is limited only to clearance and no other parameters. Strict compliance with dosing prior to collecting plasma required. Sampling times and dosing regimens need to be identical between individuals. Large numbers of subjects would be needed for this type of study because the data would be noisy. The limitation requires fairly designs otherwise leads to overestimate the variability[4, 15].

In multiple sampling designs, two or more blood samples are obtained near the trough of steady-state concentrations from most or all patients. In addition to relating blood concentrations to patient characteristics, it is possible now to separate interindividual and residual variabilities. Since patients are studied in greater detail, this design requires fewer subjects, and the relationships to patient characteristics can be evaluated with higher precision. To estimate interindividual variability of the oral clearance, nonlinear mixed-effects modeling should be used. Similar disadvantages like single trough screen also apply here[4, 15].

In full pharmacokinetic sampling design blood samples are drawn from subjects at various times over entire concentration time profile following drug administration. This approach permits an estimation of pharmacokinetic parameters of the drug in the study population and an explanation of variability using the nonlinear mixed-effects modeling approach. The full pharmacokinetic study should be designed to explore the relationship between the pharmacokinetics of a drug and demographic/pathophysiological features of the target population for which the drug is being developed[4, 15].

Population Pharmacokinetics approach

a. Population pharmacokinetics plays a key role in construction of patient dosing strategies.
b. Population pharmacokinetics approach provides integrated information on pharmacokinetics of drug.
c. Increase understanding of the quantitative relationships among drug input patterns, patient characteristics, and drug disposition.
d. Identify factors that affect drug behavior, or explain variability in a target population.
e. Used to estimate population parameters of clinical drug development.
f. Increase the efficiency and specificity of drug development by suggesting informative designs and analyses of experiments.
g. Provide information on drug safety and efficacy and drug pharmacokinetics in special populations during phase II and phase III.
h. Postmarketing surveillance.

Comparison with traditional pharmacokinetic : Population pharmacokinetic has a wide range of application in both direct patient care and drug development[2]. The estimation of the parameters engage in performing traditional pharmacokinetic studies, after single or multiple doses, in healthy volunteers or in patient's disease state. The major problem with this approach is a concern, because drug disposition in patients who receive a drug for a therapeutic effect may be significantly different from drug disposition in volunteers[5].

Compare to traditional pharmacokinetic evaluation, the population approach to pharmacokinetic assessment include the following features[14]

1. The population approach to evaluating the pharmacokinetics of a drug allows both sparsely and intensively sampled data to be used.
2. The sparse sampling approach for characterizing population pharmacokinetic yields better estimates of intersubject variability.
3. Population pharmacokinetic enables to carry out the pharmacokinetic investigations in special populations such as neonates, the elderly, patients with AIDS, critical care

patients, and those with cancer, where the number of samples to be obtained per subject is limited because of ethical and medical concerns.

4. It identify sources of variability, such as intersubject, intrasubject, and inter-occasion, as important features that should be identified and quantified during drug development or evaluation.
5. It explains variability by identifying factors of demographic, pathophysiologic, environmental, or drug-related origin that may influence the pharmacokinetic behavior of a drug.
6. It quantitatively estimates the magnitude of the unexplained part of the variability in the patient population.
7. The analyses of sparse samples collected for population pharmacokinetic analysis have been reported to be cost-effective compared with the total cost of a single Phase I study.

General Advantage and Disadvantage of Population Pharmacokinetics

Advantage [12]

1. Sparse Sampling Strategy
2. Special Populations
3. Large Number of Patients
4. Unbalanced study Design
5. Target Patient Population

Disadvantage [12]

1. Quality Control of Data
2. Timing of Analytical Results and Data Analyses
3. Complex Methodology
4. Resource Allocation
5. Unclear Cost/Benefit Ratio

CONCLUSIONS AND PERSPECTIVES

Population pharmacokinetics analysis studies are becoming gradually more significant in the areas of pharmaceutical industry and area of clinical research, especially in the drug development process i.e. Phase I, II and III clinical studies employing population kinetic analysis are often performed prior to final approval of a drug. These studies address issues related to the efficacy, toxicity and dosing of the drug in the context of a pharmacokinetic/pharmacodynamic model describing the behavior of the drug in the body and its effect. Population kinetic analysis studies are, however, extremely expensive, with the cost rising proportionally to the number of subjects involved and the complexity of the system being studied. On the other hand, knowledge of the relationship between dose, concentration, response, and pathophysiology is also essential for designing dosing strategies for rational therapeutics that may not necessarily require therapeutic drug monitoring.

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