Pharmaceutical Sciences Asia

Pharm Sci Asia 2019; 46 (2), 63-68
DOI:10.29090/psa.2019.01.018.0032

Review Article

Pharmacometrics: Alternative approach of quantitative pharmacology

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KEYWORDS:
Pharmacometrics; Population pharmacokinetics; Modeling; simulation; NONMEM; Nonlinear mixed effect modeling

ABSTRACT

The needs of understanding the pharmacokinetics and pharmacodynamics by researchers and physicians to give the best rational therapy for the patient is high. Pharmacokinetics and pharmacodynamics characteristics are usually obtained from phase one and phase two of clinical trials which are mainly involved healthy subjects and patients with restricted criteria, respectively. In special populations, such as pediatric, pregnant women, patient in critically ill condition or organ dysfunction, show different physiology condition which could alter pharmacokinetics and pharmacodynamics of the drug. Therefore, data from phase one and two of clinical trials might not represent the daily clinical practice conditions, where physicians have to prescribe drug to the patient in various conditions. On the other hand, special populations is not able to be included as subjects in clinical trials because of the ethical reasons. Therefore, pharmacometrics is an alternative method that can be used to provide pharmacokinetics and pharmacodynamics data on special populations, which more reflect daily clinical practice conditions. This method applies mathematical and statistical concept to explain the relationship between dose, plasma drug concentration, drug response and covariate factors in particular conditions. Moreover, it can be used widely in drug development processes, from *in vitro* to clinical trials.

1. INTRODUCTION

The main purpose of patient treatment is to get an optimal response with minimal adverse drug reactions. To achieve that goal, the physicians have to give the right dose for the patient, based on the pharmacokinetics and pharmacodynamics characteristics of drugs and patient's characteristics. Pharmacokinetics data are usually obtained from the result of animal study and phase one clinical trial that usually involve healthy individuals[1]. The combination of pharmacokinetics data and patient response can be used to determine the dosing regimen during drug development process and use it as an initial dose for patient treatment. In daily clinical practice, clinicians often give some particular drugs to special population groups, such as

pediatrics and geriatric patients, patients with renal failure, pregnancy and lactation female, and any other patient conditions which are not able to be included in the clinical trials. Since, their pharmacokinetics and pharmacodynamics characteristics could be dramatically different from the healthy subjects, resulted in the need for dosage adjustment[2]. On the other hand, according to some ethical reasons these populations could not be included in the clinical trials. Therefore, population pharmacokinetics-pharmacodynamics modeling and simulation are a promising approach that can be used to provide the pharmacokinetics and pharmacodynamics data and to optimize the dose for the special population. Furthermore, this method also can be used widely in all steps of drug development[2,3].

2. PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics is defined as what body does to drug, while pharmacodynamics is defined as what drug does to the body. The pharmacokinetics process can be divided into four processes, i.e. absorption, distribution, metabolism, and excretion. Absorption is a movement process from the administration site to the central compartment. Bioavailability parameter is commonly used to describe drug fraction that not changed and reaches systemic circulation. The drug bioavailability relates with its physicochemical characteristics, physiology and pathology condition of the patient, and first pass metabolism in the liver and intestine. From the systemic circulation, drug molecule will be distributed into some tissues and organs. Metabolism is a process that mainly occurs in the liver, which transforms the drug molecule becomes more polar metabolite so that can be eliminated from the body. This process is an important process to eliminate the drug from the body and terminate the biological and pharmacological activities. Excretion, especially through a kidney, will excrete the parent and/or metabolite compound of the drug.[4]

2.1. Conventional pharmacokinetics

A conventional pharmacokinetics method is usually conducted in phase one clinical trial. This study method only needs a small number of subjects (± 8-16 subjects). After subjects administer the drug, the researcher needs to collect multiple blood samples (based on half-life of the study drug) for 24 hours or more on tight schedule. Usually, the subject criteria for the conventional pharmacokinetics study are very strict and for non-toxic drug, the study normally performed in healthy subjects. This condition might not appropriately reflect the clinical practice condition of special population. Moreover, by using this method, some factors that might correlate with the pharmacokinetics parameters (for example the influence of drug-drug interaction to the pharmacokinetics profile of study drug) are not able to be added or analyzed. Hence, it is difficult to predict the impact of some factors that probably affecting the pharmacokinetics profile of the drug. Table 1 describes advantages and disadvantages of using conventional pharmacokinetics method.[5,6]

Table 1. Advantages and disadvantages of non-population pharmacokinetics

Advantages	Disadvantages
Small number of subjects (usually 10-20)	Study participants are often not represent the patient population condition
Sampling time point is often fixed and similar in all subjects	It is very rare performed in children
Use simple calculations and statistical calculation to get pharmacokinetics data	Typically need multiple blood samples (more than 10 samples per subject per day)
	It is often cannot be used to analyze quality effects of covariates
	Pharmacokinetics variability between individuals is confounded with variability in the estimate of parameters

Source: Charles B. Population pharmacokinetics: an overview. Aust Prescr. 2014;37:210-3.

2.2. Population pharmacokinetics

The population approach of pharmacokinetics and pharmacodynamics was introduced by Sheiner et al in 1971[7]. Based on this method, the pharmacokinetics profiles are obtained from high number of subjects (usually more than 40 subjects) and sometimes are collected from daily clinical practice patients[2]. The blood samples to quantify drug concentration is possible to be collected from subjects who take different dose or different administration schedule. Pharmacokinetic analysis could be done by using fewer numbers of blood samples from each subject. Hence, the correlation analysis is possible to be conducted between some covariate factors with some pharmacokinetics parameters[6]. Table 2 describes advantages and disadvantages of using population pharmacokinetics method.

Table 2. Advantages and disadvantages of population pharmacokinetics

Advantages	Disadvantages
This method is usually conducted on patient who take the drug	This method need large number of subjects
It can accommodate flexible study design	It needs complex pharmacology and statistical analysis
This method Only need few samples from each patient	Model building and model diagnostic may be complex and time-consuming
On this method we can do covariate analysis	It is difficulties with handling missing data
It can differentiate interindividual and intraindividual variability	On this method, need collection, compilation and verification large amount of data
There are some modeling software for this analysis	

Source: Charles B. Population pharmacokinetics: an overview. Aust Prescr. 2014;37:210-3.

By using this method, drug concentration will be analyzed by making population pharmacokinetics model. The model that relates between pharmacokinetics profiles to pharmacodynamics effect is known as population pharmacokinetics-pharmacodynamics model. Later in 1982, pharmacometrics term was introduced, which is a formalization of pharmacokinetics-pharmacodynamics modeling into the scientific term. Pharmacometrics is the science of quantitative pharmacology but has been more formally defined as the "science of developing and applying mathematical and statistical methods to characterize, understand, and predict a drug's pharmacokinetics, pharmacodynamics, and biomarker-outcomes behavior[8]."

2.3. Nonlinear Mixed effect modeling

Nonlinear mixed effect modeling is a method which is used to construct pharmacokinetics-pharmacodynamics models. The term nonlinear refers to a biological process (for example pharmacological response) inherently nonlinear. Hence, it is not possible to be explained using linear function[2]. Mixed effect means a combination between fixed and random effects. Fixed effects in pharmacometrics are some elements/parameters that used for the construction of a structural model and some factors that able to influence the value of the parameters. The example of the parameters is clearance and volume of distribution. Some factors that may influence pharmacokinetics parameters, such as weight, sex, dose, etc; are also known as covariate factors that used for the construction of the covariate model[6,9]. Random effects are parts of the statistical model. There are some components which quantify the variability or error in model predictions. It includes measurement error (the differences between individual prediction and observation value), interindividual variability (the differences between individual prediction and population prediction), inter-occasion variability, and unknown factors (residual variability)[9,10]. As a conclusion, the pharmacometrics model is a combination of the structural model (base model

of a pharmacokinetics-pharmacodynamics model), covariate model (built from some factors that can influence the value of the parameter in the structural model) and statistical model (explained some variation or errors in the model).

3. APPLICATION OF PHARMACOMETRICS

3.1. Application of pharmacometrics in drug development

Since this method was introduced in the 1970s, it has been widely used in every stage of drug development. In the preclinical step, it can be used for an animal study of drug's efficacy, toxicity, and interaction[3]. In the clinical trial, this method is applicable to perform descriptive and predictive population analysis, quantify optimal dose of the drug, quantify and define dosing strategy in the special populations, identification of covariate factors, and design clinical trial[10]. In addition, it also can be used in post-marketing surveillance, such as to explore or identify the unanticipated toxicity or effectiveness outcome[3].

A clinical trial is an important process in drug development. Usually, it needs huge money, a lot of subjects (dozens or thousands of subjects), long period of follow-up, and numbers of blood samples from subjetcs. Without a well-established planning process, the clinical trial could be failed and the result will not be valid to draw conclusions. Therefore, pharmacometrics method will be very useful to help the investigator constructing a model and doing simulation to optimize the clinical trial plan based on the previous data. The usage of this method can reduce cost, number of subjects and blood sample and also the length of hospitalization.[2,3]

The development process of tacrolimus is an example of pharmacometrics application in the clinical trial process. Tacrolimus is an immunosuppressive agent for the prophylaxis of organ rejection in allogeneic liver, heart and kidney transplant. The starting dose of tacrolimus was extrapolated from the result of animal studies. From several animal studies, it was predicted that the optimal starting dose was 15 mg/kg/day. Since it caused toxicity in some patients, by using the simulation, it was predicted that the reduction of 5 mg/kg/day would be optimal to reduce toxicity and maintain the effectiveness. This dose reduction was confirmed on the multicenter trial registration in United Stated and European countries. By using the pharmacometrics model and simulation, the preclinical trial result was used as a guide for planning the safe and effective for the first clinical trial in humans.[3]

3.2 Application of pharmacometrics in daily clinical practice

There are some advantages of applying pharmacometrics method in the clinical practice setting. This method can be used to define the optimal dose for special population, such as children and geriatric.[2] Pharmacokinetics study in the drug development process is usually performed in healthy adult subjects (or adult patients with specific indications for the toxic drug), so that pharmacokinetics profile in the special population is not available.[1] Clinical trials on special populations are also restricted due to the ethical reason. On the other hand, the drugs are still needed by the special population. Therefore, pharmacometrics method made it possible to analyze pharmacokinetics profile of drug in special populations, which drug concentration data obtained from sparse sample in clinical trial or routine therapeutic drug monitoring. Moreover, the pharmacokinetics profile can be used to quantify and simulate the relationship between drug concentration and response in special populations, which in the next step, it can be used to quantify the best dosing strategy for special populations.[2,3]

In the clinical trial, only "narrow" dosing regimen is used to be investigated. Unfortunately, because of some factors, good response in these dosing regimens is hard to be obtained in the patients. Pharmacometrics method is found to be useful to define the best drug concentrations-response relationship, so that this result can be used to quantify the optimal dose for patient. In addition, this method also can be used to define some clinical factors that can influence the response of the drug, so it can help physicians predict the drug response.[2]

The example of using the result of population pharmacokinetics method in daily clinical practice is showed by Zhao et al[11] who performed

population pharmacokinetics analysis to optimize dosing regimen of vancomycin in children with hematologic malignant disease. Since, different physiologic characteristic in oncologic patients might influence pharmacokinetics and pharmacodynamics of the drug. Seventy children with malignant disease were included and administered current recommended dose of vancomycin (40-60 mg/kg/day i.v). The data of trough level of vancomycin was obtained from therapeutic drug monitoring in steady state condition. Fifty-three children had subtherapeutic concentration. One compartmental model with first order elimination was fit to the data. Covariate analysis concluded that the body weight significantly influenced clearance and volume of distribution, while high of creatinine clearance also significantly increase clearance parameter. Hence, by using the patient-tailored dose method (the equation was obtained from the model), the patients who achieved target concentration were only 60%. However, this result still needed to be confirmed using prospective study to evaluate the potential clinical benefit and safety of optimized dose regimen.[11]

3.4. Challenge and benefit of pharmacometrics application in developing countries

Health problems is easily found in many developing countries, especially in the drug usage, such as high frequency of communicable diseases, the rise of antibiotic resistance, ineffective drug dose in particular population, relapse of some infection diseases, and high frequency of adverse drug reactions in drug combination for infection treatment. Most steps of drug development usually conducted in developed countries, while each country or area has their own characteristics, such as genetic characteristics, which will influence the drug response or adverse drug event. Ideally, developing countries is able to conduct their trials to solve their health problems. In fact, to conduct a clinical trial a lot of human resources, budgets, and also state-of-the-art and expensive equipment in laboratories are highly needed. Unfortunately, the resource in many developing countries are limited, so it is very difficult to provide these needs.[12]

Pharmacometrics method is very promising to be used as a tool to find solution of health problems, especially in the case that related to drug usage. For example, routine therapeutic drug monitoring is beneficial to find effective dose of digoxin for children. Although for some problems, the clinical trial still needs to be conducted, pharmacometrics method is very heplful to plan more effective clinical trial design. Moreover, data obtained from previous clinical trials is highly useful to make model and simulation to solve some problems. For example, the usage of model-based approach by Savic et al[13] in pediatric tuberculosis meningitis to find the right doses of rifampicin and levofloxacin. Population pharmacokinetics method was used in this study to analyze drug concentration data in adult with tuberculosis meningitis (rifampicin concentration in plasma and cerebrospinal fluid, and clinical outcome), and levofloxacin plasma concentration in children with tuberculosis from previous clinical trial. Besides that, pharmacokinetics value of rifampicin in children from literatures was also used. From this analysis, the best dose of rifampicin for children to achieve target drug concentration was 15 mg/kg/day intravenously or 30 mg/kg/day orally. This dose was higher than recommended dose, 15 mg/kg/day orally. Meanwhile, for levofloxacin, 19-33 mg/kg/day was the optimal dose for children to achieve the target exposure.[13]

Another advantages of applying pharmacometrics method is its cost-efficient, since only computer and software are needed. Before applying this method, having human resources with good skills on using the software and interpret the result is a must. A good collaboration among modelers, statisticians, pharmacokineticists, and other experts which related to the study drug will be beneficial to conduct the study. Reliable data is also needed to produce a valid conclusion, to put on consideration for the government to make policies related to health problems.[12]

4. CONCLUSION

Pharmacometrics is an application of mathematical and statistical method to characterize pharmacokinetics, pharmacodynamics and biomarker-outcomes behavior. The advantages of using population approach are its ability to accommodate flexible study design, reduce the number of blood samples (and other samples as well) from each subject, do covariate analysis, and differentiate interindividual

and intraindividual variability. Nowadays, this method is used widely in drug development processes and daily clinical practice, because of its inexpensiveness and minimum equipment requirement. This method is very promising and highly expected to be useful to solve many health problems in developing countries.

ACKNOWLEDGEMENTS

Conflict of interest

None to declare

Funding

None to declare

Ethical approval

None to declare

Article info:
Received June 12, 2018
Received in revised form September 1, 2018
Accepted September 30, 2018

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