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Research Article

POPULATION PHARMACOKINETICS: THEORY AND IN PRACTICAL

Arya R.S[1]., Sujitha P.J*[2]., Sambathkumar R[3] and Venkateswaramurthy N[1]

[1]Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Kumarapalayam- 638183, Tamil Nadu, India
[2]Department of Pharmacology, J.K.K. Nattraja College of Pharmacy, Kumarapalayam- 638183, Tamil Nadu, India
[3]Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam- 638183, Tamil Nadu, India

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ABSTRACT

Population pharmacokinetics can be described as the study of variabilities in plasma drug concentrations between individuals when standard dosage regimens are given with in a target population. It is concerned with measuring these variabilities within the population and to account for the patient variables includes age, sex, weight or disease state.

The determination of inter and intra subject variability regarding variance components in observed drug concentration is the principle aim of population pharmacokinetics. For the optimization of treatment inter-individual variability with respect to subject-specific covariates should also be considered. Opportunistic samples were collected from the subjects taking drug of interest and makes associations between patient characteristics and differences in pharmacokinetics can then be used to individualize drug therapy.

INTRODUCTION

Population pharmacokinetics (Pop PK) includes the study of the sources and its association of drug variabilities among individuals in the target population receiving clinically relevant doses of a drug of interest (Aarons *et al*, 1991). Patient demographical features such as age, sex, body weight, drug elimination or along with any co therapies can alter the dose-concentration relationships. For example, the patients taking treatment for renal dysfunction having more steady-state concentrations of drugs than in the patients with normal renal function who gets the same dose. By applying Pop PK measurable variable factors can be figure out and these factors can facilitates to modify the dose-concentration relationship for patient specific shifts especially in therapeutic index and dosage (Ette *et al*, 1994).

Healthy volunteers or selected patients were used to study the plasma concentration-time profile in traditional pharmacokinetics. Specific study designs such as control studies, restrictive inclusion or exclusion methods have been used to reduce the interindividual variability. Moreover, traditional pharmacokinetic study focus only on a single variable (eg. renal or hepatic function) makes it complex to study the different patient specific variables.

Pop PK approach having following features compared to traditional pharmacokinetics (Hashimoto *et al*, 1991, Ette *et al*, 2004).

- The selected subjects taken from the target population have to be treated with the drug of interest.
- The variability's noticed during drug development can be identified, measured and evaluated properly.
- The drug pharmacokinetics can be identified by analyzing patient demographics, pathophysioligical changes in subjects and environmental or associated drug related factors.
- The character of unexplained variability within the patient population can be identified.

Corresponding author:* **Sujitha P.J
Department of Pharmacology, J.K.K. Nattraja College of Pharmacy, Kumarapalayam- 638183, Tamil Nadu, India

Population pharmacokinetics development

Analyzing the drug concentration-time data produced from routine therapeutic drug monitoring can be used for improving the prescription through the approach of pop PK. Population-derived pharmacokinetic parameters such as clearance can be applied to guide prescribing for individual patients or to individualize the therapy (Perera *et al*, 2014).

Population Pharmacokinetic Modeling Methods

Different types of modeling available are (Ette et al, 1994)

Traditional structural models

Traditional structural model is applied to each individual's data. The parameters involved can be applied only in that person. This model has no assumptions on the expected distribution of residual errors for the predicted value of y. Factors with predicted noted as x and observed noted as y.$y_j = f(\theta,x_j)$, where y = j^{th} observation of y in this individual, $f(\theta,x_j)$ = parameterized curve describing an expected value for the response as a function of x for the parameter value and θ= predicted value of the response of this individual

Individual data modeling

The corresponding data model for an individual has both structural and error distributional informations can be denoted as $y_j = f(\theta,x_j) + \xi_j$ where y = j^{th} observation of y in this individual, $f(\theta,x_j)$ = parameterized curve describing an expected value for the response as a function of x for the parameter value, θ= parameter vector identifying the form of the relationship between x and y for this individual and ξ_j = zero mean measurement error. Within this individual all values of ξ_j ($\xi_{1....}$ ξ_n) comes from a series which is normally distributed and has a mean of zero.

Population data model

The corresponding data model for a population of individuals has both structural and error distributional information and in addition it has information about the distribution of θ_i between the individual in the model. It can be denoted as equation $Y_{ij} = f((\theta + \eta_i),x_{ij}) + \xi_{ij}$ where Y_{ij} = j^{th} observation of y in the i^{th} individual, $f((\theta + \eta_i),x_{ij})$ = parameterized curve describing an expected value for the response predicted by the value of x at the j^{th} observation in the i^{th} individual modified by the vector of parameter θ, θ = parameter vector identifying the form of relationship between x and y for the typical individual and η_i = zero mean variation in θ.

Statistical method

Many statistical methods has been used for the assessment of pop PK, which is summarized in Table 1.

Non linear mixed effect modeling

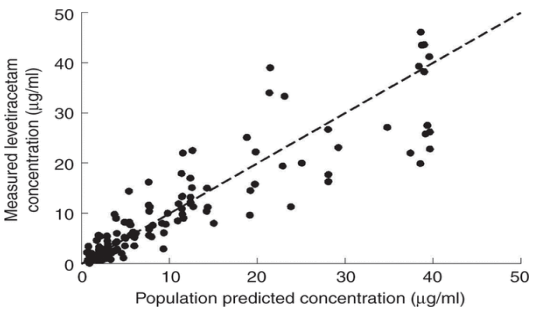
Nonlinear mixed effects modeling is performed using a software package called Non Linear Mixed Effect Model (NONMEM) version 5 it is suitable to analyze fixed effects and random effects (Johnson *et al*, 1996, Sun *et al*, 1996, Fadiran *et al*, 1996). Fixed effects (e.g. time or dose) structure the actual pharmacokinetic parameters (structural portion of model). Random effects are comprised of random interindividual variability and intraindividual variability (explainable error computed for the difference between actual and predicted concentration values) in the pharmacokinetic parameters (statistical portion of model). NONMEM provides estimation of both inter and intraindividual (i.e. residual random error) variabilities in the pharmacokinetic parameters (Prevost *et al*, 2001, Duong *et al*, 2013).

Practice of population pharmacokinetics

Pop PK modeling is a complex activity (Sheiner *et al*, 1985). It is labor intensive and time consuming. The model works by fitting the datas obtained regarding some uncertainty in the true value of the estimated parameter, so some degree of uncertainty can also attach to them.

Schematic representation of population pharmacokinetic modeling

Pop PK modeling



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Description of pharmacokinetic variabilities

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Evaluation of key PK variabilities

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Identification of relevant predictors

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Simulation of clinical scenarios

Table 1 Statistical method used in population pharmacokinetics

Parameters	Naïve pooled analysis	Two–stage analysis	Nonmem
Analysis method	Structural model, fit to all individual, even though only one is present	Structural model, fit to each individual Summarized statistically	Structural model, fit to all datas from all individual. Give inter and intravariabilities of population
Data required	Extensive or sparse within individual	Extensive within each individual	Extensive or sparse data. Uneven amount of data population can be included.
Variability in population	not available	Only available as separate statistical analysis	Available
Individual estimation	Not available	Not available	Available via Basyean approach

Examples for practical approach of Pop PK studies

Population pharmacokinetics in development of dosage nomogram for caffeine (Lee et al, 1997)

Pop PK study was conducted with NONMEM to develop a dosage nomogram for caffeine in the treatment of infants with apnoea in prematurity, and arterial blood samples of infants administered 30, 15, and 3 mg/kg caffeine citrate over 7 days by intermittent intravenous infusion were assayed using HPLC. Study showed that markedly lower drug clearance and higher volume of distribution than the previously reported values.

Optimal dosing strategy of low-molecular-weight heparins (Patel et al, 2013)

Standard dosage regimen for low-molecular-weight heparins for the treatment of antenatal venous thromboembolism is not yet known. Researchers conducted study in women who were prescribed with antenatal enoxaparin and had up to 3 anti-Xa activities withdrawn at each monthly review of subjects and used compartmental pharmacokinetic modeling using NONMEM. Subjects were administered daily dose (either once or twice daily) which is necessary for the drug to reach 3 hour plasma concentration throughout the pregnancy period and it was found that clearance and volume of distribution were increased. A significant increase in volume of distribution during pregnancy was an evident for raise in trough anti-Xa activity, when it was simulated with the progression of pregnancy period. They also found along with the progression of pregnancy the half-life of enoxaparin is also prolonged and the work provides a strong evidence for prescribing only once daily enoxaparin for the treatment of antenatal venous thromboembolism.

Population pharmacokinetic disposition of metformin in late pregnancy (Charles et al, 2006)

To study the pharmacokinetic disposition of metformin in pregnancy blood samples were collected in the third trimester of pregnancy from women with gestational diabetes or type 2 diabetes and assayed by reverse-phase HPLC method. The datas collected were fitted to two compartment, extravascular maternal model and NONMEM used for data analysis. Logarithmic interindividual and additive residual variance models were used to estimate variability between clearance and volume of distribution. They found that maternal age or weight not significantly influences the pharmacokinetics. 0.32mg/L was the variability of observed concentration from the model-predicted concentrations. The pharmacokinetics was similar to those in nonpregnant patients and, therefore, no dosage adjustment is needed. Metformin crosses the placental barrier and exposes the fetus to concentrations approaching those in the maternal circulation.

Use of tacrolimus in pediatric liver transplant recipients (Staatz et al, 2001)

The efficacy of tacrolimus in pediatric liver transplant recipients was analyzed by population pharmacokinetics using NONMEM. 35 children were taken oral immunosuppressant Tacrolimus, their datas were collected retrospectively and analyzed the typical values of apparent clearance (CL/F) and apparent volume of distribution (V/F). Study found out that there was no clear cut relation between tacrolimus dosage and blood concentrations, but most important factors that influence the pharmacokinetics of tacrolimus are the transplant type, age, and liver function test values. The study results may help physicians to individualize the therapy by considering the variabilities in pediatric liver transplant recipients.

Bayesian methodology for population pharmacokinetic analysis in drug over dose (Friberg et al, 2005)

Pharmacokinetic studies regarding drugs overdose is uncommon. A recent study used Bayesian methodology for pop PK analysis of data that taken from deliberate self-poisoning with citalopram. Researchers analyzed 14 published studies on citalopram when taken in therapeutic doses. The data set included concentration-time data from 53 patients studied after 63 citalopram overdose events (dose range: 20-1700 mg). Activated charcoal was administered between 0.5 and 4 h after 17 overdose events and having no indications of non-linear clearance after excessive doses. The final model included an estimated uncertainty of the dose amount which in a simulation study model's ability to characterize the effects of activated charcoal. There was 72% increase in activated charcoal clearance and 22% decrease in charcoal bioavailability. These findings concluded that charcoal administration is potentially beneficial after citalopram overdose. This seems to be useful for exploring the dose-exposure relationship in toxicological settings.

Population pharmacokinetics approach for regulatory process (Ette et al, 1997)

Recently using pop PK approach in new drug development and the regulatory process becomes unavoidable. Office of Clinical Pharmacology and Biopharmaceutics of the FDA conducted a survey on 206 new drug applications and supplements to find out the approach of population PK in new drug development and the regulatory process. They found that almost one-quarter (i.e.,47) of the submissions contained population PK reports, among that 83% submissions, combined clinical studies with PK studies for ensuring safety, efficacy, and dose optimization information for the drug label. Remaining 17% of the 47 application does not cause any changes in drug labeling, because the PK approach results were comparable with the previous pharmacokinetic findings.

Thus in short words pop PK methods now becomes an unavoidable part in different phases drug development process. There are much use from the pharmaceutical industry (Sheiner *et al*, 1980) and regulatory perspectives (Steimer *et al*, 1984) and web-based guidelines from regulatory agencies.(Charles *et al*, 2008, Prevost *et al*, 2001, Samara *et al*, 1997).

Population pharmacokinetics in practice

Food and Drug Administration (FDA) issued a final guidance governing the development, conduct, and analysis of population pharmacokinetic clinical trials, also states that pop PK analyses are ideal to investigate variability and alternative dosing regimens when there is prior knowledge that certain factors may affect drug behavior (US FDA, Guidance for pop PK studies, cited 2014). The need to modify the usual dose of a drug in certain populations is determined by comparing the pharmacokinetics of the sub-group to the population as a whole. In traditional method dosages are adjusted empirically across subpopulations using either clinician experience or

assuming dose proportionality with either body weight or age, these empirical approaches increase the tendency for serious adverse events or sub-therapeutic concentration levels. In order to address the inadequate dosing information, many researchers have been focusing on new approaches to pharmacokinetic analyses and model building (Steimer *et al*, 1984). Originally, pop PK modeling concentrated on the individual. Trials are restricted to representative subjects from a particular population to limit variability between subjects. An analysis of this type of data is done in two stages:

- For the first stage, plasma concentration time data are modeled using nonlinear regression to produce estimates of the pharmacokinetic parameters.
- For the second stage, the individual pharmacokinetic parameters are combined and descriptive summary statistics are computed (e.g. group mean and group variance).

Analysis of the dependencies between the parameter and any covariates use a classical statistical approach. This type of analysis moves from an individual out to the population, and as a result, the parameter estimates are unbiased and the random effects are overestimated. There are several logistical issues associated with this approach, primarily revolving around the need to perform extensive blood sampling and homogeneity of the population. These reasons have led to an alternative approach known as nonlinear mixed effects modeling (Sheiner *et al*, 1980).

A second approach to nonlinear mixed effects modeling is to directly study the pop PK, it analysis the source and correlation of variability in drug concentrations among individuals in the population. Thus method focuses on the target population and moves out to the individual. Population analyses also provide quantitative estimates of both the interindividual and intraindividual variabilities of the population. Interindividual variability may be accounted for by adding specific patient characteristics into the population model. Patient characteristics that cause changes in the dose-concentration relationship can be identified and assessed and then appropriate dosing modifications can be determined.

Drawbacks of population pharmacokinetics

There exists a false conception that population pharmacokinetics is a retreat only for when there are only very sparse data, and that the main objective should be to build models with as many covariates as possible, but neither of these views are applicable. First, there is no substitute for data obtained and while a population approach can handle sparse observational data, there are limitations also. For example each patient needed more than one data point otherwise the interindividual variability becomes unidentified. Second in terms of clinical perspective, any covariates are taken in the model only if its inclusion makes a beneficiary change in drug development. For example, in case of pharmacokinetic modeling of gentamicin renal function assessment is necessary. Besides the problem of masking more number of related covariates may occur beyond over stating a source of variability so complex models are much more difficult to implement practically and also may increase the risk of prescribing errors.

CONCLUSION

The pop PK approach is a foremost pharmacostatistical approach for studying drug character under specific clinical conditions and finally to set the individualization of drug therapy. Sparse data collected from amorphous and deranged dosing and samplings applied in this method facilitates the screening and quantifying the sources of pharmacokinetic variability. It has major advantages over traditional methods of pharmacokinetics modeling, it can handle clinically, and it has the prospective to help the adjustment of the optimum dose as per the individual needs.

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