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Population Pharmacokinetics: Principles, Methodology And Applications (General Aspects)

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ABSTRACT

Population pharmacokinetics (PPK) is an area of clinical pharmacology, which aims at the quantitative assessment of between and within individual variability in drug absorption, distribution, metabolism, and excretion. The purpose of PPK is to provide quantitative guidelines for dosage individualization / optimization. Ideally, the clinician could select an appropriate dose and dose interval once a patient has been adequately characterized by history, physical examination, and clinical laboratory tests. However, all predictive techniques are essentially imperfect. Therefore, a dosage regimen predicted for an individual may differ to some degree from the optimum regimen. Sources of variation that contribute to differences between expectation and outcome are usually categorized as interindividual and residual in nature. Even though expected parameter values can be calculated for an individual patient based on previous research and experience, the parameter values of a particular patient at hand may differ from the expected values because of interindividual variability. Residual variation includes interindividual variability (random changes in a patient's parameter from one occasion (period) to another), drug concentration measurement error, and model misspecification errors arising because all mathematical calculations for predicting parameter values are over simplifications of reality.

Key words: Population Pharmacokinetics, Interindividual variability, Residual variation.

1. INTRODUCTION

Population pharmacokinetics (PPK) is an area of clinical pharmacology, which aims at the quantitative assessment of between and within individual variability in drug absorption, distribution, metabolism, and excretion[1]. The purpose of PPK is to provide quantitative guidelines for dosage individualization / optimization[2]. Ideally, the clinician could select an appropriate dose and dose interval once a patient has been adequately characterized by history, physical examination, and clinical laboratory tests. However, all predictive techniques are essentially imperfect[3]. Therefore, a dosage regimen predicted for an individual may differ to some degree from the optimum regimen. Sources of variation that contribute to differences between expectation and outcome are usually categorized as interindividual and residual in nature. Even though expected parameter values can be calculated for an individual patient based on previous research and experience, the parameter values of a particular patient at hand may differ from the expected values because of interindividual variability. Residual variation includes interindividual variability (random changes in a patient's parameter from one occasion (period) to another), drug concentration measurement error, and model misspecification errors arising because all mathematical calculations for predicting parameter values are over simplifications of reality.

In contrast to traditional pharmacokinetic evaluation, the population approach to pharmacokinetic evaluation encompasses some or all of the following features[4].

- It seeks to obtain relevant pharmacokinetic information in patients who are representative of the target population to be treated with the drug
- It recognizes variability such as intersubject, intrasubject, interoccation variability as an important feature that should be identified and measured during drug development or evaluation.
- It seeks to explain variability by identifying factors of demographic, pathophysiological,

environmental, or drug related origin that may influence the pharmacokinetic behavior of a drug.

1.1. Background

Population pharmacokinetic is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest. 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. For example, steady state concentrations of drugs eliminated mostly by the kidney are usually greater in patients suffering from renal failure than they are in patients with normal renal function who receive the same drug dosage. Population pharmacokinetics seeks to identify the measurable pathophysiological factors that cause changes in the dose –concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified.

2. WHEN TO USE THE POPULATION PK APPROACH

In recent drug development, use of the population PK approach can help increase understanding the quantitative relationships among drug input patterns, patient characteristics, and drug disposition[5].This approaches is helpful when wishing to identify factors that affect drug behaviour, or explain variability in target population. The nonlinear mixed effects modeling approach is especially helpful in certain adaptive study designs, such as dose ranging studies (e.g., so called titration or effect conThe population PK approach can be used to estimate population parameters of a response surface model in phase 1 and late phase 2 of clinical drug development[6]. Where information is gathered on how the drug will be used in subsequent stages of drug development. The population PK approach can increase the efficiency and specificity of drug development by suggesting more informative designs and analyses of experiments. In phase 1 and, perhaps, much of phase 2, where patients are sampled extensively, complex methods of data analysis may not be needed. Two stage methods can be used to analyze the data, and standard regression methods can be used to model dependence of parameters on covariates. Alternatively, data from individual studies in phases1 and 2b can also be pooled and analyzed using the non-linear mixed-effects modeling approach.

3. POPULATION PK ANALYSIS

The framework for a more formal definition of population pharmacokinetics can be found in the population model of population analysis. The population model defines at least two levels of hierarchy. At the first level, pharmacokinetic observations in an individual (such as concentrations of drug species in biological fluids) are viewed as arising from an individual probability model, whose mean is given by a pharmacokinetic model (e.g., a bi exponential model) quantified by individual-specific parameters, which may vary according to the value of individual-specific time varying covariates. The variance of individual pharmacokinetic observations (intrasubject variance) is also modeled using additional individual-specific pharmacokinetic parameters.

3.1. Analysis Plan

There should be a prospectively written analysis plan for the population PK analysis. The analysis plan should be presented and could form an appendix in the report of the population PK analysis. It is acknowledged that the level of information in the analysis plan may be less detailed than in a standard clinical protocol, due in part to the exploratory nature of some population analyses [7]. However, the analysis plan should at least include:

- The objective(s) of the analysis
- A brief description of the study (or studies) from which the data originate
- The nature of the data to be analyzed (how many subjects, rich or sparsely sampled)
- The procedures for handling missing data and outlying data
- The general modeling aspects (e.g. software, estimation methods, diagnostics)
- The overall modeling procedure/strategy
- The structural models to be tested (if this has been decided)
- The variability models to be tested
- The covariates and covariate models to be tested together with a rationale for testing these covariates based on, for example, biological, pharmacological and/or clinical plausibility.
- The algorithms/methods to be used for covariate model building
- The criteria to be used for selection of models during model building and inclusion of covariates. (e.g. objective function value, level of statistical significance, goodness of fit plots, standard error, inter-individual variability, clinical relevance)

- The model evaluation/qualification procedures to be used

References to specific methodologies used should be given, and when relevant included in the documentation submitted.

3.2. The TWO-STAGE Approach

The traditional method of pharmacokinetic data analysis uses a two-stage approach. The first stage of this approach involves the estimation of pharmacokinetic parameters through nonlinear regression using an individual's dense concentration-time data (data-rich situation). Individual parameter estimates obtained during the first stage serve as input data for the second-stage calculation of descriptive summary statistics on the sample, typically, mean parameter estimates, variance, and covariance of the individual parameter estimates. Analysis of dependencies between parameters and covariates using classical statistical approaches (linear stepwise regression, covariance analysis, cluster analysis) can be included in the second stage. The two-stage approach, when applicable, can yield adequate estimates of population characteristics. Mean estimates of parameters are usually unbiased, but the random effects (variance and covariance) are likely to be overestimated in all realistic situations[8].

3.3. The Nonlinear Mixed-Effects Modeling Approach

When properly performed, population PK studies in patients combined with suitable mathematical/statistical analysis, for example, using nonlinear mixed-effects modeling, is availed, and on some occasions, preferred alternative to extensive studies. In sparse data situations, where the traditional two-stage approach is not applicable because estimates of individual parameters are, a priori, out of reach, a single-stage approach, such as nonlinear mixed-effects modeling, should be used.

4. STUDY DESIGN AND EXECUTION

The population PK approach is useful for looking at the influences of physiological as well as pathophysiological conditions on parameters of a model with a well-established structure. The qualitative aspects of the model should be well known before embarking on a population PK study. When a population PK study is proposed, certain preliminary pharmacokinetic information and the drug's major elimination pathways in humans already should be known. Preliminary studies should establish the basic pharmacokinetic model of the drug because the sparse data collected during population PK studies may not provide adequate information for discriminating among pharmacokinetic

5. SAMPLING DESIGNS

In the population pharmacokinetics context, three broad approaches (with increasing information content) exist for obtaining information about pharmacokinetic variability: (1) the single-trough sampling design, (2) the multiple-trough sampling design, and (3) the full population PK sampling design.

5.1. Single-Trough Sampling Design

In the single-trough sampling design, a single blood sample is obtained from each Patient at, or close to, the trough of drug concentrations, shortly before the next dose[9[and a frequency distribution of plasma or serum levels in the sample of patients are calculated. Assuming that the sample size is large, the assay and sampling errors are small, and the dosing regimen and sampling times are identical for all patients, a histogram of the trough screen will give a fairly accurate picture of the variability in trough concentrations in the target population. If the three conditions are not met, a histogram will not represent strict pharmacokinetic variability because the data will include other sources of random fluctuation that significantly contribute to the observed spread[10]. When related to therapeutic outcome and occurrence of side effects, such histograms can provide information about the optimal concentration range of a given drug.

When implementing single-trough sampling, the difficulty of getting patients and physicians to adhere to the sampling strategy should be kept in mind. Compliance with at least the last two doses before trough level measurement should be sufficient for this type of study, but the drug should be dosed to steady state. Because of possible uncertainties in compliance and sample collection times, method can be reasonably applied only to drugs dosed at intervals less than or equal to one elimination half-life, unless the timing and level of the dose can been surged, as in inpatient studies[11]. Large numbers of subjects would be needed for this type of study because the data would be noisy.

5.2. The Multiple -Trough Sampling Design

In the multiple-trough sampling design, two or more blood samples are obtained near the trough of steady-state concentrations from most or all patients. In addition to relating blood concentration to patient characteristics, it is possible now to separate interindividual and residual variabilities. Since patients are studied in greater detail in this design, the design requires

fewer subjects, and the relationship of trough levels to patient characteristics can be evaluated with greater precision. To estimate interindividual variability in clearance, nonlinear mixed effects modeling should be used. When using pharmacokinetic models for parameter estimation, a sensitivity analysis[12].

5.3. The Full Population Pk Sampling Design

The full population PK sampling design is sometimes called experimental Population pharmacokinetic design or full pharmacokinetic screen. When using this design, blood samples should be drawn from subjects at various times (typically 1 to 6 time points) following drug administration[13]. The objective is to obtain, where feasible, multiple drug levels per patient at different times to describe the population PK profile. 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.

6. IMPORTANCE OF SAMPLING INDIVIDUALS ON MORE THAN ONE OCCASION

The variance of the pharmacokinetic observations of an individual about the individual specific pharmacokinetic model on a given occasion (i.e., the intra-individual variability)can be factored conceptually into two components: (1) variability of pharmacokinetic observations due to variability of the pharmacokinetic model from occasion to occasion(interoccasion variability) and (2) variability of pharmacokinetic observations about the individual pharmacokinetic model appropriate for the particular occasion (noise; pharmacokinetic model misspecification).

7. SIMULATION

Simulation is a useful tool to provide convincing objective evidence of the merits of a proposed study design and analysis[14]. Simulating a planned study offers a potentially useful tool for evaluating and understanding the consequences of different study designs. Short comings in study design result in the collection of uninformative data. Simulation can reveal the effect of input variables and assumptions on the results of a planned population PK study. Simulation allows study designers to assess the consequences of the design factors chosen and the assumptions made. Thus, simulation enables the pharmacometrician to better predict the results of a population PK study and to choose the study design that will best meet the study objectives[15,16]. A simulation scheme should entail repetitive simulation and appropriate analysis of data sets to control for the effect of sampling variability on parameter estimates. Alternative study designs may be simulated to determine the most informative design.

8. STUDY PROTOCOL

Two types of protocol, add-on and stand-alone protocols, may be considered depending on the setting in which a population PK study is to be performed. In either case, the protocol should contain a clear statement of the population analysis objectives, as well as details of the proposed sampling design and data collection procedures. The specific pharmacokinetic parameters to be investigated should be identified in advance. If the population PK study is added on to a clinical trial (add-on study), as can be envisioned in most situations, the PK protocol should be carefully interwoven with the existing clinical protocol to ensure that it does not compromise the primary objectives of the clinical study[17].

8.1. Population pharmacokinetic study protocol

The practical details of pharmacokinetic evaluation should be described in a population pharmacokinetic study protocol, although the principles may be specified on the clinical study protocol in a general way. The primary (same as that in the clinical protocol) and secondary objectives should be clearly stated. The secondary objectives should be those that enable the data analyst to search for the unexpected, after the primary objectives have been addressed. The sampling design, data and data anomalies should be clearly spelled out in the protocol. The data to be used for population analysis should be defined, including patients and subgroups to be used and covariates to be measured.

8.2. Population pk study as add-on protocol

When the population PK study is an add-on to a primary clinical study, the objectives of the population PK study should be defined clearly. The objectives should not compromise the objectives of the primary clinical study. The criteria for sampling subjects and the methods for data analysis (described in the population PK study protocol) should be stated clearly. The data to be used for population analysis should be defined[18] including patients and subgroups to be used and covariates to be measured. The sampling design should be specified and any subpopulation stratification should be defined.

8.3. Stand-Alone study protocol

When a population PK study is a stand-alone study, the study protocol should describe the practical details of the pharmacokinetic

evaluation. The primary and secondary objectives of the population PK study should be stated clearly. The secondary objectives should be those that enable the data analyst to search for the unexpected, after the primary objectives have been addressed. The sampling design, data assembly, data checking procedures, and procedures for handling missing data and data anomalies should be clearly spelled out in the protocol. The data to be used for population analysis should be defined[19] including patients and subgroups to be used and covariates to be measured.

9. STUDY EXECUTION

A population PK study should be conducted according to current good clinical practice (GCP) and good laboratory practice (GLP) standards. It is important to take all reasonable measures to ensure accurate information on dosing and timing of samples relative to dosing history. The sampling strategy and the recording of samples should be part of good clinical practice and the handling of samples is part of good laboratory practice. Errors in recording sampling times relative to dosing history could result in biased and imprecise parameter estimates, depending on the nature and degree of the error[20].

10. ASSAY

Correct evaluation of pharmacokinetic data depends on the accuracy of the analytical data obtained. The accuracy of analytical data depends on the criteria used to validate the assay method and on the quality of the sample. The importance of using validated assay methods for analyzing pharmacokinetic data cannot be over emphasized. Consequently, drug and/or metabolite(s) stability, assay sensitivity, selectivity, recovery, linearity, precision, and accuracy should be carefully scrutinized before samples are analyzed. Consideration should be given to having the assays for population PK done with minimized assay variability. To ensure quality of the sample, clinical investigators and their staff should be educated on the importance of proper labeling and handling of biological samples.

11. DATA HANDLING

11.1. Data assembly and editing

Real-time data assembly prevents the problems that generally arise when population PK data are stored until the end of a clinical trial. Real-time data assembly permits an ongoing evaluation of site compliance with the study protocol and creates the opportunity to correct violations of study procedures and policy[21,22]. Evaluation of pharmacokinetic data can provide the safety data monitoring board with insight into drug exposure safety evaluations and drug-drug interactions. Real-time data assembly creates the opportunity for editing the concentration-time data, drug dosing history, and covariates data in a timely manner to meet the pharmacokinetic objectives of a clinical trial and to facilitate the model building process.

11.2. Handling missing data

After assembling data for population analysis, the issue of any missing covariate data should be addressed. Missing data will not automatically invalidate the results provided a good-faith effort is made to capture the missing data and adequate documentation is made regarding why data are unavailable. However, missing data represent a potential source of bias. Thus, every effort should be made to fulfill the protocol requirements concerning the collection and management of data, thereby reducing the amount of missing data. Many subjects may be rich in covariate data, and some may be missing only a small sample of covariates.

12. OUTLIERS

The statistical definition of an outlier is, to some extent, arbitrary. The reasons for declaring a data point to be an outlier should be statistically convincing and, if possible, prespecified in the protocol. Any physiological or study-related event that renders the data unusable should be explained in the study report. A distinction should be made between outlying individuals (intersubject variability) and outlier data points (intrasubjectvariability). Because of the exploratory nature of population analysis, the study protocol may not specify a procedure for dealing with outliers. In such a situation, it would be possible to perform model building on the reduced data set (i.e., the data set without outliers) to reanalyze the entire data set (including the outliers) using the final population model, and to discuss the difference in the results. Including extreme outliers is not a good practice when using least-squares or normal-theory type estimation methods; as such outliers inevitably have a disproportionate effect on estimates.

13. DATA TYPE

All data along a spectrum between two extreme types of data can be used in population PK analysis. The extremes are represented by experimental data and observational data. Experimental data arise from traditional pharmacokinetic studies characterized by controlled conditions of drug dosing and extensive blood sampling. Observational data are

collected, most often, as a supplement to a study designed and carried out for another purpose. Such data are characterized by minimal control and few design restrictions (e.g., the dosing history is subject specific; the amount of pharmacokinetic data collected from each subject varies; the timing of blood sampling in relation to drug administration differs; and the number of samples per patient, typically 1 to 6, is small).

14. POPULATION PK MODEL DEVELOPMENT

14.1. Objectives, Hypothesis, and Assumptions

The objectives of the analyses should be stated clearly. The hypothesis being investigated should be articulated clearly. It is recommended that all known assumptions inherent in the population analysis be explicitly expressed (e.g., model assumptions, including forms and distributions of interindividual random effects and residual errors[23].

14.2. Model Building (Population Model Development)

The steps taken (i.e., sequence of models tested) to develop a population model should be outlined clearly[24] in the population analysis report to permit the reproducibility of the analysis. The criteria and rationale for model building procedures dealing with confounding, covariate, and parameter redundancy should be stated clearly. The criteria and rationale for model reduction to arrive at the final population model should be explained clearly.

14.3. Reliability of results

The reliability of the analysis results can be checked by careful examination of diagnostic plots, including predicted versus observed concentration, predicted concentration superimposed on the data, and posterior estimates of parameter versus covariate values. Checking the parameter estimates, standard errors, case deletion diagnostics, and sensitivity analysis may also be appropriate. Confidence intervals (standard errors) for parameters may be obtained by using either nonparametric techniques (such as the jackknife (25) or the profile likelihood plot (mapping the objective function[26].

14.4. Model Validation

The objective of model validation is to examine whether the model is a good description of the validation data set in terms of its behavior and of the application proposed. Validation can be defined as the evaluation of the predictability of the model developed (i.e.,the model form together with the model parameter estimates) using a learning or index data set when applied to a validation data set not used for model building and parameter estimation.

Validation depends on the objective of the analysis. A model may be valid for one purpose and invalid for another. There is no right or wrong model, nor is there a right or wrong method of fitting; subjectivity, therefore, plays a large role in model choice, validation, and interpretation of results. Currently, there is no consensus on an appropriate statistical approach to validation of population PK models. The choice of a validation approach depends on the objective of the analysis because the model is both unknown and complex (subject to multiplicity of unknown covariant effects, and nonlinear).

14.5. Cross-Validation

Cross-validation which is the use of repeated data-splitting may prove beneficial because (1) the size of the model development database can be much larger than in alternative validation methods, so that less data are discarded from the estimation process, and (2) variability is reduced by not relying on a single sample split. Due to high variation of estimates of accuracy, cross-validation is inefficient when the entire validation process is repeated[27].

14.6. Bootstrapping

Bootstrapping, another way to perform re sampling, has the advantage, like cross validation, of using the entire data set for model development. Because the sample size is limited in pediatric settings where ethical and medical concerns prevent recruitment into studies, bootstrapping can be especially useful for evaluating the performance of a population model if there is no test data set[28].

14.7. Validation Methods

14.7.1. Prediction errors on concentrations

Prediction errors on concentrations are calculated as the difference between observed and model-predicted concentrations. The mean prediction error is calculated and used as a measure of accuracy, and the mean absolute error (or root mean square error) is used as a measure of precision.

14.8. Standardized prediction errors

Calculation of standardized prediction errors (29) takes into account variability and correlation of observations within an individual. The mean standardized prediction error and the variance are calculated, and a test (a to z test) is performed to determine whether the mean is significantly different from zero and the standard deviation approximates.

14.9. Plotting residuals against covariates

Plotting residuals against covariates is a method related to the prediction errors on concentration approach; the method differs in the sense that no statistic is computed and no statistical tests are performed. A simple plot of residuals obtained by freezing the final model and predicting into a validation data set against covariates can yield information on the clinical significance of the model in terms of a covariate or subpopulation[30].

15. Validating through parameters

The validation-through-parameters method[31] avoids the problems encountered in prediction error of concentrations by performing validation with model parameters. Model parameters are predicted from the validation data set with or without covariates, and bias and precision are calculated for the predictions.

16. Determining posterior predictive check

A new method, the posterior predictive check, may prove useful in determining whether important clinical features of present and future data sets are faithfully reproduced by the model[32]. However, this approach has not been widely used.

17. POPULATION PK STUDY REPORT

17.1. Summary

The summary should provide an overall summary of the population PK study. It should include enough information on the context of the study and an indication of the population PK study's findings and conclusions.

17.2. Introduction

The introduction should briefly state the general intent of the study. It should include enough background information to place the population PK study in its proper context within the drug's clinical development and indicate any special features of the population PK study.

17.3. Objectives, Hypotheses and Assumptions

The objectives of the study and analysis should be stated clearly following the introduction section of the report (33). In addition to the primary objective, any secondary objectives should be explicitly stated. If modifications are made in the objectives of the study after acceptance of the protocol, those changes should be noted in the population PK report. The report should state clearly what assumptions have been made and what hypotheses tested.

17.4. Materials and Methods

This section should contain the study protocol. In a case where data from multiple studies are pooled for analysis, the applicable study protocols should be referenced. The study design, planned sample sizes, and patient selection information, which would contain selection criteria and specific center information, should also be included. Information about the medication (the drug, dose, timing of doses, and compliance) should be documented[34]. Assay and data collection and analysis methods should be described in detail.

17.5. Assay

This section should contain a description of the assay method(s) used in quantitating drug concentrations. Assay performance (quality control samples), sample chromatograms, and standard curves should also be included. The validity of the method(s) should be described[35].

17.6. Data

The report should contain the response variable and all covariate information and explain how they were obtained. The report should include a description of the sampling design used to collect the plasma samples and a description of the covariates, including their distributions and, where appropriate, the accuracy and precision with which they were measured. An electronic copy of the data set should be submitted (36). Data quality control and editing procedures should be described in this section.

17.7. Data Analysis Methods

This section should contain a detailed description of the criteria and procedures for model building and reduction, including exploratory data analysis. The following components of the data analysis method used in the study should be described here: (1) the chosen population analysis method, (2) the assumptions on model components (e.g., parameterization, random effects distributions), (3) the rationale underlying those assumptions, and (4) the chosen model-fitting method. In addition, this section should contain a description of the treatment of outliers and missing data (where applicable), as well as a flow diagram(s) (if possible) of the analysis performed and representative control/command files for each significant model building/reduction step.

17.8. Results

The key results of the analysis should be compiled in comprehensible tables and plots. Diagnostic plots used to develop the model and test reliability should be included. To aid interpretation and application, a thorough description of the results should be provided.

Complete output of results obtained for the final population model and key intermediate steps should be included.

17.9. Discussion

The report should include a comprehensive statement of the rationale for model building and reduction procedures, interpretation of the results, protocol violations, and discussion and presentation of supporting graphs. The consequences of the modeling should also be discussed (e.g., suggested dosing according to body weight, relationship of Creatinine clearance to drug clearance, and impact on special populations).

17.10. Application of Results

A discussion of how the results of the analysis will be used (e.g., to support labeling, Individualize dosage, safety, or to define additional studies) should be provided. A discussion of the relationship between statistical significance and clinical relevance should also be included.

17.11. Appendix

The appendix should contain a representative portion of the data set used in population analysis. The programming codes along with the printouts of the results of the final model should be included, as well as any additional plots that are deemed important. Whether the analysis was performed as a result of an add-on clinical study or a standalone population PK study, the study protocol should be included in the appendix.

17.12. Electronic Files

FDA is currently finalizing a guidance for the electronic submission of NDAs, which will include information on how to submit the population PK study report in electronic format.5 In addition, FDA is actively working on standardizing data file formats for population PK and other clinical pharmacology data and will include these standards in future versions of the electronic guidance document

18. LABELING

Where population model parameter estimates are included in the label, the total number of subjects used for the analysis and the precision with which the parameters were estimated should be included. Where the results of the population PK analysis provide descriptive information for the label, it should be stated that the information was obtained from a population analysis

19. ADVANTAGES OF POPULATION APPROACH

- PK-PD information about drug in target population.
- Better estimates of population mean and variance.
- Estimates and explain variability in drug response.
- Opportunity to assess multiple factors influencing disposition (covariate combinations).
- Assess performance of dosage adjustment in target population.
- Assess relationship between exposure / (concentration, Cmax, AUC) and efficacy (pain relief, time to onset of action, need for rescue medication).
- Assess effects of demographics, concomitant medication, and pathophysiology on the exposure –response relationship.

20. LIMITATIONS /CHALLENGES OF THE POPULATION APPROACH

- Data are often from non-controlled clinical situation

  -Attainment of quality data
- Complexity of population PK methodologies

  -Time –consuming and computer intensive
- Specific expertise is needed

Collaboration with individuals across multiple disciplines

21. CONCLUSIONS

Population pharmacokinetic offers a wide range concept to measure the inter and intra individual variability among the individuals. By performing the population pharmacokinetic study one optimize the dosage according individuls pharmacokinetic parameters and reduce the dose related toxicities and providing cost effective therapy for the patients. In this review we highliting the basic methodology, principles and applications of population pharmacokinetics

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