Introduction to Population Pharmacokinetic modeling

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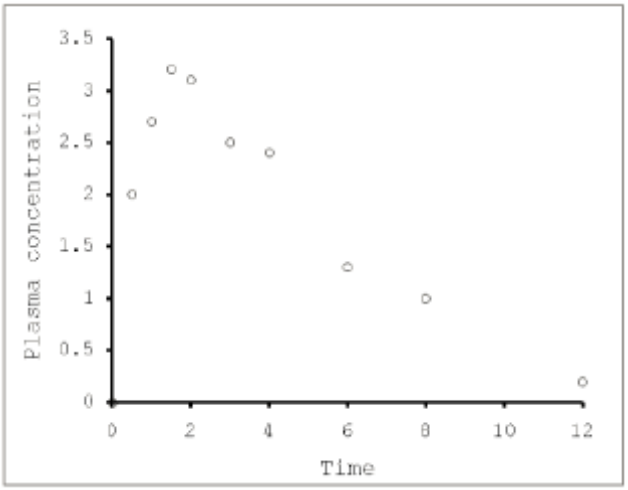
No conflicts of interest to report

Questions:

- Population PK is the description of the PK of an individual in a population. Yes (red) or No (green)
- Non-compartment analysis is suitable to study the influence of physiological changes on the of behaviour of the drug. Yes (red) or No (green)
- PK curves of healthy volunteers are aimed at model identification (red) or identification of interindividual variability (green)

Typical data in an individual PK curve



Non-compartmental pharmacokinetic analysis

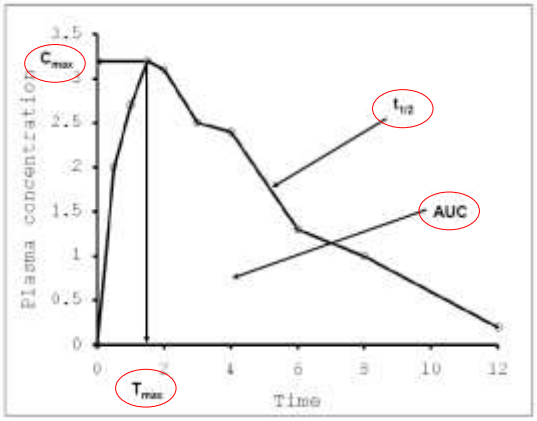
Advantage:

-Simple

Disadvantage:

- Only descriptive

- Not suitable for study of the influence of physiological changes on the of behaviour of the drug



Compartmental pharmacokinetic analysis

Advantage:

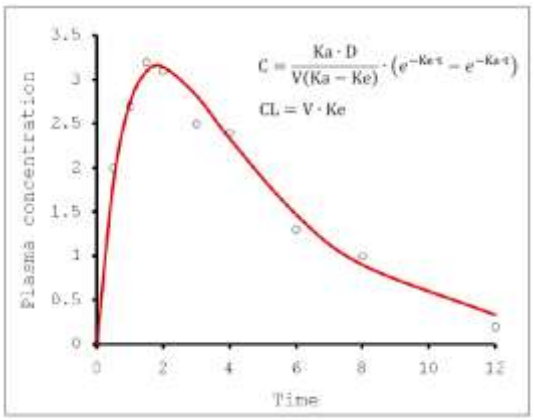
- Can be used for mathematical modelling in other doses and patients

Disadvantage:

- Requires mathematical and physiological understanding

-Requires software

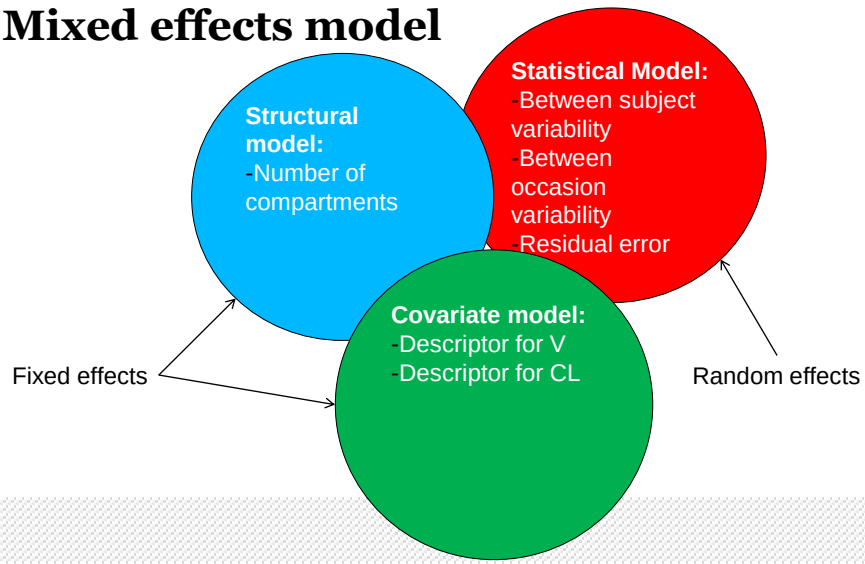
-Takes more time



Population Pharmacokinetics is

- A description of pharmacokinetic behaviour of a drug in a population
  - Using a pharmacokinetic model, describing the typical relationships between physiology and pharmacokinetics
- A description of the interindividual variability in these relationships
  - Using a statistical model for parameter distribution and error

Mixed effects model



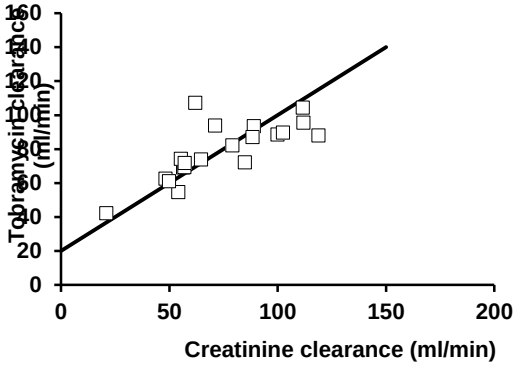
Population modeling allows you to:

- Find interindividual characteristics on PK
  - Covariates like renal function, pharmacogenetics
- Find interoccasion or intraindividual variability
  - Bioavailability, alterering renal function
- Find other sources of error
  - Model misspecification
- Define MAP Bayesian parameter estimation
  - for dose adjustment in individual patient (TDM)

Model parameters

- Model parameters
  - Measure of central tendency (‘mean value’)
  - Measure of inter-individual variability (‘sd’)
  - Covariance between parameters (often ignored!)
  - Assessment of covariates

CL = CLm + fr . CLcr



Parameter distribution

- Parametric methods require assumptions, e.g.
  - normal distribution
  - log-normal distribution
- Nonparametric methods

Data (measurements)

- Rich data
- Sparse data

Rich data

- Large number of blood samples from each subject
- Small number of subjects
- Experimental environment
- Healthy volunteers

- Aim: model identification

Sparse data

- Small number of blood samples from each patient
- Large number of subjects
- Clinical environment
- Patients

- Aim: Identification of model parameters and covariates for TDM

Methods

- Naive pooling
- Standard Two-Stage (STS)
- Mixed-Effect modeling (eg: NONMEM)
- Nonparametric methods (eg: NPEM)
- Iterative Two-Stage Bayesian (ITSB)

Naive Pooling

- Data of all patients pooled
- Inter-individual variability ignored
- No information on inter-individual variability obtained

Standard Two-Stage (STS)

Step 1

Data of each patient analysed separately

Step 2

Mean and SD of model parameters calculated from results of step 1

Standard Two-Stage (STS)

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- Conceptually and computationally simple

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- Inter-individual variability overestimated
- Not applicable to sparse data
- Problems with ‘non-fittable’ patients

Mixed-Effect Modeling

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- Statistically sophisticated
- Generally accepted (FDA)
- Inter- and intra individual variability estimated
- Rich and sparse data

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- ‘Black box’

Iterative Two-Stage Bayesian

- Prior knowledge of parameter distribution is needed to estimate posterior distribution
- Assume a reasonable set of population data (e.g. from STS)
  - means ± sd
  - covariance matrix (usually zero)
  - residual error (e.g. assay error pattern)

Iterative Two-Stage Bayesian

- Step 1: Perform Bayesian analysis on each subject separately

- Step 2: Calculate new set of population data
  - means ± sd
  - covariance matrix
  - residual error

Iterative Two-Stage Bayesian

› Repeat step 1 and step 2 until convergence is reached, i.e.

stable values for:

- means ± sd
- covariance matrix
- residual error

Iterative Two-Stage Bayesian

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- Conceptually and computationally simple

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- Results may be less precise and/or less accurate for sparse data

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Literature

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