


Pharmacokinetics and Pharmacodynamics

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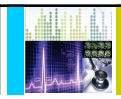
What is PK/PD?




- Inter-disciplinary field
  - Biostatistics
  - Pharmacokinetic/Pharmacodynamic modeling.
  - Computational methods

Outline

- Basic terminology
  - PK parameters
  - PD
  - Population PK
- What do we get from PK/PD modeling and simulations
- The model
- Example – The appropriate dose for children
- Fitting the model and estimating the parameters
- Model Evaluation
- Simulations

What is PK?

Pharmacokinetics (PK) includes the study of the mechanisms of absorption and distribution of an administered drug, the rate at which a drug action begins and the duration of the effect, the chemical changes of the substance in the body (e.g. by enzymes) and the effects and routes of excretion of the metabolites of the drug.

PK parameters

- **Half life**: The half-life is the time taken for the plasma concentration to fall to half its original value. The symbol is $T_{1/2}$ and the units are Time units.
- **AUC** is the area under the concentration time curve and has the units of concentration by time units.
- **Clearance**: Clearance can be defined as the volume of plasma which is completely cleared of drug per unit time. The symbol is CL and the units are Volume units/Time units
- **Blood Volume of Distribution**: The volume of distribution is used to quantify the distribution of a medication between plasma and the rest of the body after dosing. It is calculated as the ratio of the total amount of drug in body and the concentration of drug in Blood. The symbol is Vd and has Volume units.

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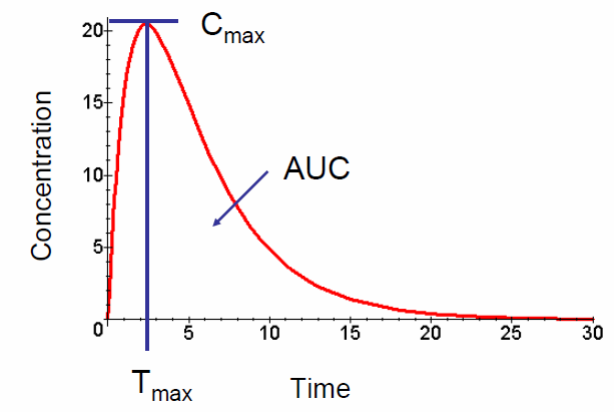
PK Parameters



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What is PD?

Pharmacodynamics (PD) is the study of the physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect
.
Pharmacokinetics is often studied in conjunction with pharmacodynamics. Pharmacodynamics explores what a drug does to the body, whereas pharmacokinetics explores what the body does to the drug.

PD parameters

- The PD parameters depend on the kind of the measured PD
- PD parameters are clinical in their nature
- Examples can be EC50, disease progression, disease activity, etc.

Population PK analysis

- investigate and identify fixed effect sources of variability (covariates) which influence the PK and PD of a drug.
- Estimate the magnitude of the inter-individual variability
- Estimate the random residual variability (including intra-individual, measurement error), partially addressing the question of whether a drug effect is highly variable.
- Population pharmacokinetic analysis requires the use of non-linear mixed effects models.
- PK-PD modeling is sub-area of population pharmacokinetic analysis

Benefits of PK-PD analysis

- Modeling the relation between the PK of the drug and the PD that is in interest
- Decision making (for example, which dose should be used in the next study, dosing intervals etc.)
- Risk analysis – What will be the effect size? What is the probability of success?
- Extrapolation from one population to another – for example from adults to children

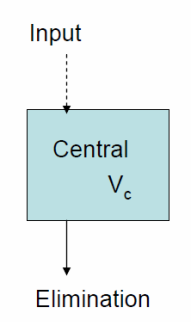
PK modeling

- Goal: model the drug concentration in the blood as a function of time
- Parameters of the model can be V, CL, $t_{0.5,}$ etc

The one compartment model

- This is one of the simplest model: one compartment with first-order elimination.
- Other options – two or more compartments, non-linear PK and more

$$C = \frac{D}{V} \cdot \exp\left\{-\frac{CL}{V} \cdot t\right\}$$



PD model

- This can be done in many ways, depending on the knowledge about the disease and the drug mechanism of action
- The simplest model is the direct response model:

$$E = E_0 + E_{\max} \cdot \frac{C}{C + EC_{50}}$$

Combining PK and PD

- We want to examine the relation between C (concentration) and PD levels.
- Since C is modeled using PK parameters (CL, V etc.), the final model will include all PK parameters and all PD parameters
- This will result in a non-linear random effect model

Non-linear model with random effects

- Dependent variable – PD Response
- Independent variable - time from dosing
- Model parameters

  The model depends also on a vector of individual parameters, such as volume of distribution, clearance, etc.

  Usually we will be interested to estimate two types of model parameters, the average value and the population variability of these parameters. We still will define these two as model parameters we want to estimate.
- Covariates

Population variability

- Between subject variability in model parameters
  - Model parameters have fixed and random effect part
  - Each patient will have its own deviation from the mean from which a variance can be estimated for each model parameters. These variances define the between subject variability.

$$Cl = Cl_{fixed} + Cl_{random}$$

Population average: $C = \frac{D}{V}\exp(-(\frac{Cl_{fixed}}{\mathrm{V}}\mathrm{t})$

Specific individual: $C = \frac{D}{V}\exp[-(\frac{Cl_{fixed} + Cl_{random}}{\mathrm{V}})\mathrm{t}]$

Intra-individual variability

- Within subject variability in response is mainly related to the measurement noise.
- It is also a random effect within an individual.
- It occurs at the observation level.

$$C_{obs_{i,j}} = C + \varepsilon_{i,j}$$

$C_{obs_{i,j}}$: Observed concentration for individual i, j^{th} observation

$\varepsilon_{i,j}$: random effect quantifying the measurement noise

Example – Pediatric dose

- Objectives
  - What is the pediatric dose that would achieve the same exposure as in adults (PK)
  - What is the pediatric dose that would reach a given value of a surrogate marker of efficacy (PD)
- Challenges with Pediatric data
  - It is easier to collect samples in adults than in children/infants/neonates
  - The usual extrapolation based on weight is more difficult to make when using only weight as parameters when going from adults to children/infants, especially for clearance
- What Pharmacometrics can do?
  - Taking the pooled adult/children/infants/neonates data and provide a mathematical/statistical framework that will allow learning optimally about children/infant Pharmacokinetic characteristics
  - Use that new model based information to predict efficacy in children/infants/neonates

Example – Pediatric dose

- Clinical Trial for patient population from age 1 month to 16 years old
  - Antiepileptic Drug X
  - Very few PK data for the infants
  - Richer PK information for adolescents
- Single Dose escalation study
- IV Route
- PK model: one compartment model with V and CL as model parameters
- Prior information suggests average Clearance expressed by an Emax type of equation (PD model)

Building the model

- PK model: $c = \frac{D}{V}\exp\left(-\frac{Cl}{V}t\right)$

- Random effects: Usually, log-normal distribution is assumed for PK parameters, hence:

$$Cl = Cl_{fixed} \cdot \exp\left(Cl_{random}\right)$$
$$Cl_{random} \sim N(0, \sigma^2_{Cl})$$

(will be additive in the log scale)

Building the model

- Covariates:
  - BW- body weight
  - MF- maturation factor (takes values between 0 and 1 represents the fraction of adult typical function. There is a formula to calculate MF for a given age.

$$V_{fixed} = V_{std}\left(\frac{BW}{70}\right)^{1}$$

$$Cl_{fixed} = Cl_{std}\left(\frac{BW}{70}\right)^{0.75} \cdot MF$$

V_{std} and Cl_{std} are typical clearances and volumes for an adult weighing 70kg.

Combining all parts together

$$Cl = Cl_{std}\left(\frac{BW}{70}\right)^{0.75} \cdot MF \cdot \exp(Cl_{random})$$

$$V = V_{std}\left(\frac{BW}{70}\right) \cdot \exp(V_{random})$$

$$c = \frac{D}{V}\exp\left(-\frac{Cl}{V}\cdot t\right) = \frac{D}{V_{std}\left(\frac{BW}{70}\right)\exp(V_{random})}\exp\left(-\frac{Cl_{std}\left(\frac{BW}{70}\right)^{0.75} \cdot MF \cdot \exp(Cl_{random})}{V_{std}\left(\frac{BW}{70}\right)\exp(V_{random})}\cdot t\right)$$

$$Cl_{random} \sim N(0, \sigma_{Cl}^2)$$
$$V_{random} \sim N(0, \sigma_V^2)$$
$$\varepsilon \sim N(0, \sigma^2)$$

Model fitting and estimation

- There are several methods to find maximum likelihood estimates in non-linear mixed effects modeling (each software uses different method, the best method depends also on the structure of the model):
  - The first order approximation - the nonlinear regression model is linearized via a first-order Taylor series expansion and is evaluated at the expected value of the random effects, 0.
  - Conditional estimation procedure -The random effects value for each individual is estimated using empirical Bays method, first order conditional expansion, laplacian conditional estimation or hybrid estimation.
  - Expectation-maximization algorithm
  - MCPEM (Monte-Carlo parametric expectation-maximization algorithm)
  - Discrete nonparametric maximum likelihood
  - Continuous nonparametric maximum likelihood
  - Bayesian inference using Gibbs sampling

Model evaluation

- Check assumptions and model fit – scatter plots, review outputs.
- Check if the model consistent with existing theories and prior knowledge.
- Examine predictive performance:
  - Internal validation – Same overall data set as data used in model building: data splitting, cross validation.
  - External validation – Use entirely new data set
  - Check prediction vs. observed values, residual vs. time, residual vs. prediction.
- Bootstrap – Used to obtain distribution of parameter estimates – standard errors, confidence interval.
- No standard method applies for all models. The choice of model checking method should be made a priori and should be guided by modeling objectives

PK/PD Simulations

After the model was fitted and found to be valid, the estimates can be used to simulate a new trial with different design and "examine" its results.

- Simulation of a clinical trial can provide a data set that will resemble the results of an actual trial.
- Multiple replications of a clinical trial simulation can be used to make statistical inferences

1. Estimate the power of the trial
2. Predicting p-value
3. Estimate the expected % of the population that should fall within a predefined therapeutic range.
   - Help decide on the optimal dose.
   - Can support go/no go decisions.

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Simulation stages

1. Generate random numbers for the fixed effects, if any, based on the estimates and its SE.
2. Generate random numbers for the covariates, if any, based on knowledge about the covariates in the relevant population
3. Generate random numbers for the random effects for each subject based on the estimated variance parameters of the random effects.
4. Calculate the value of the PK or PD variables based on the numbers in stages 1-3 and the model.
5. Repeat stages 1-4 multiple (1000-5000) times
6. Calculate the expected value/confidence intervals for the desired PK/PD/response variable