Application of Population Modeling and Optimal Design

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Outline

• Introduction
  • Clinical Pharmacology
  • Pharmacometrics

• NONMEM – Population PK modeling
  • What is modeling?
  • What is NONMEM?
  • How to do a population analysis.
  • Why are covariates important?
  • What is Allometric scaling?
  • How do I know my model is right?
Outline

- Optimal Experimental Design
  - Determining sample size
  - Optimization of design
- Example application of Population PK modeling and Optimal Design
  - Pioglitazone in Septic Pediatric Patients
- Summary
Clinical Pharmacology
Translational research

Clinical information/observation

Data

Patients

Research techniques
- Analytical
- PK/PD/PG modeling & simulation

PK/PD/PG – pharmacokinetic, pharmacodynamic, pharmacogenetic
Pharmacokinetics & Pharmacodynamics

**Pharmacokinetics** - movement of a drug from “absorption” to “elimination”. What the body does with the drug.

**Pharmacodynamics** - how the drug works at the target tissue. What the drug does to the body.
Pharmacogenetics

Genes Determine Drug Effects

- Assists in prediction of response
- Explains variability in response
- Role of genotyping in prescribing?
Pharmacometrics
“The science of interpreting and describing pharmacology in a quantitative fashion, through modeling and simulation”

Pharmacokinetics

\[ CL, V, Ka \]

Pharmacodynamics

\[ E_{max}, EC_{50} \]

Pharmacometrics involves the development and application of mathematical and statistical methods to characterize, understand and predict a drug’s PK, PD and biomarker – outcome behavior

- Determine typical population response
- Understand and quantify variability in PK and response
Dose Individualization

• Complicated due to differences
  – Cellular response
  – Metabolism
  – Receptor number and type
  – Enzymes
  – Absorption
  – Genetics

• “Utilization of PK, PD and PG techniques allows for quantification of the uncertainty associated with information related to drug behavior and rationalization of decisions in making dosing changes for individuals, thereby personalizing medicines”
Population Approach

“A means to study sources and correlates of variability in drug responses (concentration and/or effect) among individuals representative of those in whom the drug will be used clinically”
Why is a population approach useful?

• Used to obtain relevant PK information from a study group who are representative of the target population the drug is used in.

• Allows for variability to be identified and measured drug development and during drug use.

• Variability can be explained by recognizing the factors that may influence PK behavior such as:
  – demographic, pathophysiological, environmental or drug-drug interaction
  – These are the predictable components of between subject variability (BSV)
• Can also estimate the magnitude of the unexplained variability in the subject population
  – This is the random component of BSV
• Used when undertaking studies in a clinic:
  – in outpatients, elderly patients, surgical patients, obstetrics and in children and neonates
• For drug development studies:
  – All phases of drug development (phase I, II and III) to aid in improving subsequent clinical development
• Type of analysis may also be required for registration of a pediatric drug
• Useful when analyzing observational data
  – collected from routine clinical practice or from a study that had few design restrictions
  – PK data may be supplemental in a study, which was designed for another purpose

• Using observational data may limit model development due to restrictions in the study design
  – Application of optimal experimental design can be used to provide guidance for when taking samples
Advantages or disadvantages of approach?

**Advantages**

- May only need a small number of measurements or observations from each subject
- Can be cheaper to obtain
- Subjects contributing to the data set may better reflect the target population of the drug
Disadvantages

• Data quality may be poor and may have too much process noise due to subject compliance e.g. outpatient studies

• Data collected from retrospective reviews or in multicenter clinical trials (phase II) may also be of poor data quality

• Relatively large numbers of subjects are required
NONMEM

- Software program using nonlinear mixed effects modeling (NONMEM)
  - Accepted standard population analytical approach
  - Sparse/rich, unbalanced/unstructured data
  - Uses the population as the unit for the PK analysis (rather than a single individual)
  - However individuality of the subjects is maintained
What is NONMEM?

- Written in FORTRAN
- Two major components
  - NM-TRAN (NONMEM Translator)
    - a preprocessor that translates inputs specified in a more “user-friendly” way to the formats required by NONMEM
  - PREDPP (“PRED for Population Pharmacokinetics”)
    - Specialized PRED subroutine for use with NONMEM for pharmacokinetic data
    - Collection of FORTRAN subroutines
What does NONMEM do?

- NONMEM - used to analyze data using a NONlinear Mixed Effects Model
  - Focus on population pharmacokinetic data, however, can handle several other problem sets as well
  - Nonlinear regression (e.g., extended least squares ~ maximum log likelihood)
  - Mixed effects models have 2 or more components
    - Mixed effect modeling allows for the fixed effects (mean values) effects and random values (variability) to be simultaneously quantified
The language of NONMEM

Parameters

- THETA ($\theta$) = population mean parameter (typical values)
- OMEGA ($\omega$) = between subject variability/variance (BSV)
- SIGMA ($\sigma$) = residual unexplained variability/variance (RUV)

Random effects

These are not parameters in a population model.

- ETA ($\eta$) = the difference of an individual from the population average (variance ($\eta$) = $\omega$)
- Epsilon ($\varepsilon$) = the difference of an observation from a model prediction (variance ($\varepsilon$) = $\sigma^2$)
Approach to using NONMEM

• Build a basic structure of a process “structural model”
  – built using equations, which include THETAs which describe the PK parameters and are estimated by NONMEM and fixed effects

• Two models to describe random “stuff” which results in noise/error in measurements
  – random effects are described using normal distributions of randomness e.g. the intersubject variance model and the intrasubject variance model
What are mixed effects?

- **Fixed effects**
  - Typical values of clearance, volume of distribution or covariates
    - eg weight has a “fixed effect” on clearance

- **Random effects**
  - Termed random as they can not be predicted in advance. Two types of random variability related to biological data:
    - Between subject variability related to CL or V etc.
      - one individual is different from another individual and is not related to noise or error
    - Residual variability (assay error, model misspecification, process noise etc.)
      - difference between the prediction of the model for the individual and the measured observation, also called intra-individual or within-subject variability
What is the objective function value?

• Generated during every NONMEM run
• The sign or magnitude in itself is not useful. The change in the OFV when comparing different models is important*
• A decrease in the OFV value means a “better” fit of the model to the data (provided the data set is unchanged)
  *Larger negative values describe better fits to values closer to zero
What are covariates?

• Covariate models
  – Explain BSV in parameters and response using patient covariates
  – Improve predictive performance
  – Understand causes of variability

• Patient covariates
  – Demographic (weight, age, height, gender, ethnicity)
  – Biomarkers (renal/hepatic function)
  – Concomitant medication (beta-blocker, CYP inhibitors)
  – Comorbidity (other diseases)
How to develop a model

![Flowchart of model development process]

1. **Base Structural Model**
2. **Base Covariate Model**
3. **Diagnostic Plots**
4. **Univariate Analyses**
5. **Add Most Significant Covariate to Form New Base Model**
6. **Full Multivariable Model**
7. **Evaluate IV and RV Models**
8. **Base Multivariable Model**
9. **Remove Most Non-significant Covariate to Form New Base Multivariable Model**
10. **Univariate Backward Elimination**
11. **Final Model**

**Decision Points:**
- **No Significant Covariates?**
- **All Remaining Covariates Significant?**
What is Allometric scaling?

• Models scale weight by relating it to body functions and morphology
• In biology metabolic and structural characteristics (e.g. tissue mass) scale predictably with $\frac{3}{4}$ power functions of weight
• Allometric model that uses a $\frac{3}{4}$ power model is favoured in PK models for pediatrics and is thought to explain discrepancies in variability using other functions
How do I know my model is right?

- Are the fixed effects parameter values realistic?
- Convergence difficulties, warnings/run messages
- $COV$ fails
- Stability (rerun with different initial estimates)
- Over-parameterisation
  - diminishingly small variances (e.g. < 10^{-4})
  - large imprecision (SE of estimation high)
  - simplify the model
  - structural components
  - random effects components
Model evaluation

- Model fit – objective function value
- Internal vs. external validation
- Bootstrap or cross-validation methods
- Goodness of fit plots
  - TIME vs DV
  - PRED vs DV
  - PRED vs WRES or CWRES
  - TAD vs WRES
  - IPRED vs DV
- Predictive checks – simulate data from final model and check against raw data
Other available Pop PK software

- P-PHARM, WinNonMix, NPEM, WinBugs, Monolix
- Also NPML, MC-SIM and Stochastic EM – but these are not used to any great extent
Optimal Experimental Design
Optimal Design

• Objective of optimal design is to:
  – utilize population PK modeling
  – use variability estimates
  – account for significant covariates
  – suggests rational sparse sampling strategy
Optimal Design

• Population PK modeling and optimal sampling strategies use programs like WinPOPT (v. 1.2) or ADAPT (v.5)

• To evaluate and to determine an optimal sampling strategy in a population.

• This is based on the Population Fisher Information Matrix of nonlinear mixed effects models
Optimal Design

• Precision of the estimated parameters in PK/PD studies can be correlated with sampling design
• Relationship has lead to the development of design metrics, which can provide the optimal design or determine the most precise parameter estimates
• Term optimal applies when discussing a maximally informative design as determined by using any appropriate method
• One example of a design metric is the D-optimality criterion
D-optimal design

- D-optimality was the design criterion utilized (the determinant of the inverse Fisher information matrix was the scalar that was optimized)
- The D-optimality product criterion used to determine the sampling strategy is the Fisher Information Matrix (FIM), equation

\[ D_P(\psi, \Xi) = \prod_{k=1}^{2} |M_F(\Psi^k, \Xi)|^{1/P_k} \]

Where, MF is the FIM, \( \psi^k \) is the vector of all population parameters, \( P_k \) represents the number of parameters in the kth model and \( \Xi \) is the population design

Duffull et al. (2005) J Pharmacokinet Pharmacodyn
Optimal design methods needs prior knowledge:

1. Type of structural PK model (e.g., one, two, or three compartment models; and for orally administered drugs with first order absorption)

2. Estimates of the PK parameters (e.g., absorption rate constant (ka), clearance (CL), volume of distribution (Vd))

3. Distribution of inter-individual variability for the PK parameters and estimates of the variance for each of the distributions

4. Residual variability model and the associated variance

5. Study design: (sampling constraints, maximum number of potential recruits, maximum number of samples per patient, timing between samples)
Clinical Trial Design
Clinical trial design

Types:
- Treatment trial
- Prevention trial
- Screening trial
- Quality of life trial

Clinical Trial Design

Optimal design

Modeling and Simulation

Clinical outcome

Basic research

Data collection

Subjects

Prospective
Randomized
Cross-over
Double-blinded
Clinical trial design

Types:
- Treatment trial
- Prevention trial
- Screening trial
- Quality of life trial

Types of Clinical Trials:
- Treatment trial
- Prevention trial
- Screening trial
- Quality of life trial

Basic research
Data collection
Subjects
Budget

Modeling and Simulation
Optimal design
Clinical outcome
Prior Experience
Regulatory Experience

Prospective
Randomized
Cross-over
Double-blinded

Clinical Trial Design

Clinical outcome
Optimal design
Prior Experience
Regulatory Experience
Modeling and Simulation
Types: Treatment trial
Prevention trial
Screening trial
Quality of life trial

Prospective
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Basic research
Data collection
Subjects
Budget
Example of application of Population PK Modeling and Optimal Design

Optimal Study Design for Pioglitazone in Septic Pediatric Patients

Introduction

• Pioglitazone (PIO) – a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist
• Primarily known as a thiazolidinedione anti-diabetic agent which increases insulin sensitivity
• Inhibits monocyte inflammatory cytokines involved in regulation of sepsis-induced inflammatory response
• Reported to exert anti-inflammatory effects in experimental models of sepsis and improve survival
• May reduce inflammatory process associated with severe sepsis in pediatric patients

Eckland et al. (2000) Exp Clin Endocrinol Diabetes
Jiang et al. (1998) Nature
Zingarelli et al. (2003) J Immunol
Objective

• Primary objective was to design a single dose PK study for pioglitazone in pediatric patients with severe sepsis:
  – utilizing population PK modeling
  – variability estimates
  – significant covariates
  – rational sparse sampling strategy
  – never tested in children previously
Pharmacokinetics

- Limited data was available from a single dose study in adolescents with type 2 diabetes
  - AUC ng•h/mL (min, mean, max for single 15, 30 and 45 mg)
  - Time-concentration profiles means (single dose 15, 30 and 45 mg)
  - Samples Pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 48 hours

- PK parameters from literature
  - mean half-life 8-9 (4-17 h)
  - Vd/F 0.253 (0.199–0.299 L/kg)
  - CL/F 2.4 (1.72-4.17 L/h)
  - Ka 0.4-1.17 h⁻¹

Christensen et al. (2005) J Clin Pharmacol
Table 1  Comparison of PK estimates for a single dose between the literature reported values and simulated values for 15, 30 and 45 mg

<table>
<thead>
<tr>
<th></th>
<th>Half-life (h) mean (range)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml) mean (range)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (ng h/ml) mean (range)</th>
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</thead>
<tbody>
<tr>
<td>Christensen et al. [16]</td>
<td></td>
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<tr>
<td>15 mg</td>
<td>8–9 (4–17)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>478 (333–886)</td>
<td>4506 (2849–7522)</td>
</tr>
<tr>
<td>30 mg</td>
<td>8–9 (4–17)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>587 (120–1225)</td>
<td>5618 (1076–8868)</td>
</tr>
<tr>
<td>45 mg</td>
<td>8–9 (4–17)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1053 (701–1715)</td>
<td>10438 (6297–16897)</td>
</tr>
<tr>
<td>Simulated PK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg</td>
<td>7.9 (4.9–11.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>498 (357–870)</td>
<td>4933 (2534–8094)</td>
</tr>
<tr>
<td>30 mg</td>
<td>8.3 (5.29–13.3)</td>
<td>629 (343–1156)</td>
<td>5563 (2134–9142)</td>
</tr>
<tr>
<td>45 mg</td>
<td>9.3 (5.18–16.95)</td>
<td>1087 (589–1743)</td>
<td>10663 (4784–20134)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reported half-life mean (range) for single dose (15, 30, 45 mg)

<sup>b</sup> Estimated half-life mean (range) for single dose (15 mg)

Fig. 4 Flow diagram showing methods used in study design. Where PK is pharmacokinetic; AUC is area under the curve; T1/2 is half-life; Cmax is maximum plasma concentration.
In pediatric studies, when a power equation to determine sample size or sampling, a 20% CV in the parameter of interest is considered the quality standard.

*Fig. 5* Using PFIM estimates obtained relating to sample size required for 2–6 years 15 mg. Where CV is coefficient of variation; BSV is between subject variability, CL is clearance; $V_d$ is volume of distribution and $K_a$ is absorption rate constant.
Conclusions

• PK of pioglitazone described and data simulated
• D-optimal design strategy provided sample times (0.5, 2, 6 and 21 h for 24 h dose)
• Pioglitazone not previously used to treat sepsis in 1-18 year old patients, potential risks
• Dosing will need to be individually assessed and evaluated
• Study is currently recruiting
Summary

• Modeling and Simulation techniques provide not only answers but novel ways to understand complex situations

• Optimal Design allows accurate and analyzable collection of data with fewer samples

• Personalizing dosing provides an ability to take current information and improve care
Acknowledgements

Work undertaken at CCHMC, Cincinnati, Ohio

Prof. Michael Spigarelli
Dr Lili Ding
Dr Jennifer Kaplan
Prof. Alexander Vinks

Support was provided by a NIAMS T32
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Thank you for inviting me

Any questions?