Pharmacometrics
Application of Modeling & Simulation to Pediatric Drug Studies & Individualized Dosing

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Pharmacometrics

the Science of Quantitative Pharmacology

- Use of models based on pharmacology, physiology and disease for quantitative analysis of interactions between drugs and patients
- This involves PK, PD and disease progression with a focus on populations and variability
- To better predict and control exposure and response in individual patients
- Achieve paradigm shift in way we do pediatric clinical drug studies

http://en.wikipedia.org/wiki/Pharmacometrics
Pharmacometrics & Systems Pharmacology

Integration of model-based drug discovery and development

Systems Biology ↔ Systems Pharmacology ↔ Translational Sciences ↔ Exposure Response ↔ Optimized Medicines

‘Right Pathway’ ↔ ‘Right Target’ ↔ ‘Right Molecule’ ↔ ‘Right Dose’ ↔ ‘Right Patients’

Impact

Van der Graaf Editorial PSP-CPT 2012
Why Pediatric Pharmacometrics

- Off-label use of 50-60% in children and up to 90% in (premature) neonates
- Missing information on Pharmacokinetics, Efficacy and Safety
- Lack of informative pediatric drug labels
- Missing age-appropriate dosage forms for the pediatric population
Informative PK/PD Study Design

Getting the Dose right

How many patients?

How many samples

Modeling & Simulation
How to Double Success Rate of Pediatric Trials?

Simulate2Design

Model4Approval

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Developmental Pharmacology Concepts

- Growth and development are two linked co-linear processes in children
- Size standardization is achieved by allometric scaling
- Age is used to describe maturation of clearance
Mechanistic Basis of Using Body Size and Maturation to Predict Clearance

Acetaminophen clearance

Maturation of GFR and other drugs

Model-based Trial Design

Prior Knowledge
PK/PD Model

Clinical Trial Simulation

Scenario Analysis
Dose Selection

Learn & Confirm

change the outcome®
How modeling and simulation can help in the design of pediatric studies

- Development of a population PK/PD/PG model using newly generated or prior knowledge
- Simulation of ‘realistic’ virtual patients
- Simulation of the virtual clinical study
  - How many patients & how many samples
  - What are the best times for sampling
- Optimizing of trial design and data analysis method prior to the study
Development of Population Model based on prior knowledge

- Population analyses
  - Non-compartmental (WinNonlin)
  - One-compartmental model (NONMEM)
    - Absorption model with/without lag time
- Covariates e.g. WT, AGE, PGx
  - Allometrically scaled: \( CL = CL_{std} \times (WT/70)^{0.75} \)
- Variability components
  - IIV on all parameters except F and lag time
  - IOV on bioavailability, Ka and lag time
- Simulations
  - Across age range
  - Sample from realistic age-weight distribution

From available data

From literature & available data

From available data
Determining Sample Size

- How many patients?
  - Required number of patients for statistically robust estimation of PK/PD relationship(s)
- How many samples per patients?
- What best times to sample
  - Optimal sampling strategies
How to get Best Estimates?

• Create a design that will yield the smallest confidence region

Powering Population PK studies

- Power equation to determine sample size or sampling, a 20% SE has been proposed as the quality standard

Gobburu, Pediatric advisory committee meeting, 2009
Jacqmin, J&J Pediatric Symposium, 2005
The study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for DRUG NAME in each pediatric sub-group with at least 80% power.
Sample Size Calculation for PopPK Analysis

- Sparse/Rich PK sampling design
- Nonlinear mixed-effect modeling & clinical trial simulation is generally needed to derive the appropriate sampling schedule and the sample size.
- FDA quality standard:
  - Calculate the 95% CI for a derived parameter such as CL when a covariate model is applied for this parameter

\[ CL_i = CL_{pop} \cdot \left[ \frac{WT_i}{70\text{kg}} \right]^{0.75} + \eta_{CL,i} \]
Sample Size Requirements based on FDA criterion

Sample size to achieve 95% upper Cl ≤ 1.4 * Mean

Variability (% CV)
Table 2: Sample sizes per age group for three drugs submitted as a part of a BPCA pediatric exclusivity program. The failure to meet the proposed quality standard is indicated by “Pass CL?” and “Pass V?”. For the failed groups, the ratio of 95% upper CI and the mean are presented.
Case study
Teduglutide PK/PD in Pediatric Patients with Short Bowel Syndrome

- Teduglutide - a synthetic glucagon-like peptide-2 analog
  - evaluated for treatment of short-bowel syndrome (SBS)
- Design Pediatric multiple-dose Phase-I clinical study
  - determine safety, efficacy and PK of teduglutide in pediatric patients with SBS aged 0-12 months
- Application of clinical trial simulations
  - novel generalized additive modeling approach for location scale and shape (GAMLSS)
  - facilitates simulating population specific demographic covariates
- Goal was to optimize likelihood of achieving target exposure and therapeutic effect
  - based on observations in adult patients

Development of Pediatric Population Model

- Structural 3-compt PK model with oral absorption (NONMEM)
  - Healthy volunteers (IV data)
- Allometric scaling component on clearance (CL) and volume of distribution (V)
- Model modified to include glomerular filtration rate (GFR) maturation as part of TDG clearance change over time
  - \( MF = \frac{PMA^{Hill}}{TM50 + PMA^{Hill}} \)
  - TM50 is the maturation half-time

\[
CL_i = CL_{\text{adult}} \cdot \left( \frac{WT_i}{WT_{\text{adult}}} \right)^{0.75}
\]

Where \( CL_i \) is Clearance of the individual, e.g. child or neonate.
Expressed as L/h/70Kg
Generating Realistic Covariates

- SBS patients have body weights below the 5th quantile of their respective age groups.
- GAMLSS modeling was used to simulate age-matched body weights values below the 5th quantile (R code).

GAMLSS: Generalized Additive Models for Location, Scale and Shape
Predicted Teduglutide Exposure based on Clinical Trial Simulations
Clinical Trial Simulation results
Teduglutide dosing strategy to achieve optimal target attainment

- Dose reductions of 55, 65, 75, and 85% in the 0–1-, 1–2-, 2–3-, and 3–6-month age groups, compared with the optimal dosing regimen in the 6–12-month age group.
- Percentages of patients with steady-state teduglutide exposure within the targeted window of efficacy.
Continuing Paradox of Drug Development

1. Clinical trials provide evidence of efficacy and safety at usual doses in populations

\[
\begin{array}{c}
\text{Efficacious & Safe} \\
+ \\
\text{Efficacious & Safe}
\end{array}
\]

2. Physicians treat individual patients who can vary widely in their response to drug therapy

\[
\begin{array}{c}
\text{No Response} \\
+ \\
\text{Efficacious & Safe} \\
\rightarrow \\
\text{Adverse Drug Reaction}
\end{array}
\]
DASHBOARDS
Web-based decision support for individualized immunosuppression

What if we had pharmacokinetic and pharmacogenetic data, …adherence data and … protocol recommended drug exposure targets and … patient reported outcomes (side effects) and … passive patient reported outcomes…
all in the same place?

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Ahna Pai, PhD - Center for Treatment Adherence
Alexander A. Vinks, PharmD, PhD - Clinical Pharmacology

Supported by a Place Outcomes Award
One Dose Does Not Fit All
Large variability at standard doses

MPA AUC (mg・hr/L)

Kidney

Heart

Liver

Target

Target

MMF Dose, 1 g BID

## Bayesian Estimation

### Prior Probability
- Population Model

### New Info
- Concentration Biomarker

### Objective Function
- Consider Prior + New

### Posterior Probability
- Individual Model

### Goals
- Look at Patient
- Think

### Control
- Select drug
- Calculate Dose

\[ \Phi_2 = \sum_{i=1}^{n} \left( \frac{C_i - E_i}{S_i} \right)^2 + \sum_{k=1}^{m} \left( \frac{\theta_k - \mu_k}{\sigma_k} \right)^2 \]

Courtesy: Roger Jelliffe, MD, USC, Los Angeles

Thomas Bayes 1702 - 1761
Target-Controlled Model-Based Individualized Dosing

- Patient data
- PK/PD/PG Population Model
- Check Target Attainment and Response
- Patient
- Targeted Dosing

Disease progression – improvement & Outcomes measures
Individualized Mycophenolate Mofetil Dosing Based on Drug Exposure Significantly Improves Patient Outcomes After Renal Transplantation

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- APOMYGRE (Multicenter study, France):
- Randomized study evaluating model-based Bayesian dose adjustments
- 11 centers, 137 patients - first year post-transplantation
- Primary outcomes parameter: treatment failure
- Acute rejection - Graft loss – Death - GI, infections and hematological AEs
Adherence system is based on the MEMS monitor
Prototype Dashboard MMF
Real life application of M&S

Participating Centers

Patient visit
Sample collection
UPS shipment
Web/email notification

Centralized LC-MS/MS Analysis

Confirmation
Dose change

Bayesian estimation
Dosing recommendation
Uploaded to web
Email notification

Results reported
On Web
Email notification
Sent out
Model-based decision support

- Dose adjustment based on Bayesian feedback
- Capturing of maturation of clearance and changes over time
  - Disease progression/improvement
  - Other factor e.g. infections
Conclusions

• Modeling and simulation are powerful tools for the design of informative PK/PD studies

• With relative little data, and application of literature information it is possible to make informed decisions on pediatric study design

• Implementation of D-optimal design will increase information content and improve the cost-effectiveness of studies

• Model-based dosing (Bayesian estimator) is the way forward in ‘personalized’ clinical trials
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