POPULATION PHARMACOKINETICS

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Population Pharmacokinetics

Definition

Advantages/Disadvantages

Objectives of Population Analyses

Impact in Drug Development

Definition

Population pharmacokinetics describe

- The typical relationships between physiology (both normal and disease altered) and pharmacokinetics/pharmacodynamics,
- The interindividual variability in these relationships, and
- Their residual intraindividual variability.

Sheiner-LB
Definition

E.g.: A simple Pk model

\[ C_P = \frac{R_i}{C_l} \left( e^{-\frac{t}{k} - \frac{t}{e}} \right) \]

- \( R_i \): infusion rate
- \( C_l \): drug clearance
- \( k \): elimination rate constant
- \( \varepsilon \): measurement error, intra-individual error

\( \varepsilon \approx N(0, \sigma) \)

Definition

\[ C_P = \frac{R_i}{C_l} \left( e^{-\frac{t}{k} - \frac{t}{e}} \right) \]

\[ C_P = C_{P_{\text{e}}} \cdot \left( e^{-\frac{t}{k} - \frac{t}{e}} \right) \]

\[ C_l = \frac{R_i}{C_{P_{\text{e}}}} \pm \varepsilon \]

Definition

\( C_l = \text{metabolic clearance} + \text{renal clearance} \)

\( C_l = \Theta_1 + \Theta_2 \cdot C_{Cr} \pm \eta \)
Cl = metabolic clearance + renal clearance
Cl = Cl metabolism + Cl kidney

\[ \eta \approx N(0, \omega) \]

Graphical illustration of the statistical model used in NONMEM for the special case of a one compartment model with first order absorption. (Vozeh et al. Eur J Clin Pharmacol 1982;23:445-451)

Objectives
1. Provide Estimates of Population PK Parameters (CL, V) - Fixed Effects
2. Provide Estimates of Variability - Random Effects
   - Intersubject Variability
   - Interooccasion Variability (Day to Day Variability)
   - Residual Variability (Intrasubject Variability, Measurement Error, Model Misspecification)
Objectives

3. Identify Factors that are Important Determinants of Intersubject Variability
   - Demographic: Age, Body Weight or Surface Area, gender, race
   - Genetic: CYP2D6, CYP2C19
   - Environmental: Smoking, Diet
   - Physiological/Pathophysiological: Renal (Creatinine Clearance) or Hepatic impairment, Disease State
   - Concomitant Drugs
   - Other Factors: Meals, Circadian Variation, Formulations

Advantages

- Sparse Sampling Strategy (2-3 concentrations/subject)
  - Routine Sampling in Phase II/III Studies
  - Special Populations (Pediatrics, Elderly)
- Large Number of Patients
  - Fewer restrictions on inclusion/exclusion criteria
- Unbalanced Design
  - Different number of samples/subject
- Target Patient Population
  - Representative of the Population to be Treated

Disadvantages

- Quality Control of Data
  - Dose and Sample Times/Sample Handling/Inexperienced Clinical Staff
- Timing of Analytical Results/Data Analyses
- Complex Methodology
  - Optimal Study Design (Simulations)
  - Data Analysis
- Resource Allocation
- Unclear Cost/Benefit Ratio
Models are critical in sparse sampling situations:
Models are critical in sparse sampling situations:
APPLICATIONS

Study Objectives

• To evaluate the efficacy of pregabalin or placebo as add on treatment in patients with partial seizures.

Data Structure

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Doses Explored</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>308</td>
<td>0, 600 mg/day (bid &amp; tid)</td>
</tr>
<tr>
<td>2</td>
<td>287</td>
<td>0, 150, 600 mg/day (tid)</td>
</tr>
<tr>
<td>3</td>
<td>447</td>
<td>0,50,150,300,600 mg/day (bid)</td>
</tr>
<tr>
<td>Total</td>
<td>1092</td>
<td></td>
</tr>
</tbody>
</table>
### Count Model

\[ P(Y_i = x) = e^{-\lambda} \frac{\lambda^x}{x!} \]

\( \lambda \) represents the expected number of events per unit time.

\[ \text{E}(Y_i) = \lambda_i \]

The natural estimator of \( \lambda \) is the overall observed rate for the group.

\[ \hat{\lambda} = \frac{\text{Total counts}}{\text{Total time}} \]

Suppose there are typically 5 occurrences per month in a group of patients: \( \lambda = 5 \)

<table>
<thead>
<tr>
<th>( x )</th>
<th>Pr(( Y = x ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.007</td>
</tr>
<tr>
<td>1</td>
<td>0.034</td>
</tr>
<tr>
<td>2</td>
<td>0.084</td>
</tr>
<tr>
<td>3</td>
<td>0.140</td>
</tr>
<tr>
<td>4</td>
<td>0.175</td>
</tr>
<tr>
<td>5</td>
<td>0.180</td>
</tr>
<tr>
<td>6</td>
<td>0.150</td>
</tr>
<tr>
<td>7</td>
<td>0.104</td>
</tr>
<tr>
<td>8</td>
<td>0.065</td>
</tr>
<tr>
<td>9</td>
<td>0.036</td>
</tr>
<tr>
<td>10</td>
<td>0.018</td>
</tr>
</tbody>
</table>
The mean number of seizure episodes per month ($\lambda$) was modeled using NONMEM as a function of drug dose, placebo, baseline and subject specific random effects.

$$\lambda = \text{Baseline} + \text{placebo} + \text{drug} + \eta$$

Baseline = estimated number of seizures reported during baseline period
Placebo = function describing placebo response
Drug = function describing the drug effect
$\eta$ = random effect

**Initial Model**

$$\lambda = \text{BASE} \cdot \left(1 - \frac{E_{\text{max}} \cdot D}{ED_{50} + D} - \text{PLAC}\right) \cdot e^{\eta}$$

$$\lambda = 10.8 \cdot \left(1 - \frac{0.38 \cdot D}{48.7 + D} - 0.1\right) \cdot e^{\eta}$$

- BASE = 10.8 [9.9, 11.7]
- ED$_{50}$ = 48.7 [11.3, 129.1]
- $E_{\text{max}}$ = 0.38 [0.15, 0.61]
- PLAC = -0.1 [0.22, 0.52]
- $\eta$ = 1.1 [0.3, 1.98]

**Sub-population analysis**

- Some patients are refractory to any particular drug at any dose.
- Interest is in dose-response in patients that respond
- Useful in adjusting dose in patients who would benefit from treatment
- Investigate the possibility of at least two sub-populations.
Mixture Model

A model that implicitly assumes that some fraction \( p \) of the population has one set of typical values of response, and that the remaining fraction \( 1-p \) has another set of typical values.

**Population A (p)**

\[ \lambda_1 = \text{Baseline}_1 + \text{placebo}_1 + \text{drug}_1 + \eta_1 \]

**Population B (1-p)**

\[ \lambda_2 = \text{Baseline}_2 + \text{placebo}_2 + \text{drug}_2 + \eta_2 \]

---

**Final Model**

- **PopulationA = 75%**
  \[ \lambda = 11.1 \cdot \left(1 - \frac{1}{186 + \text{Dose}} \cdot D_1 - 0.11 \cdot D_0\right) \cdot e^{\eta} \]

- **PopulationB = 25%**
  \[ \lambda = 15.1 \cdot \left(\eta + 0.26 \cdot D_1 + 1.44 \cdot D_0\right) \cdot e^{\eta} \]
Expected percent reduction in seizure frequency

- Monte Carlo simulation using parameters and variance for Subgroup A
- 8852 individuals (51% female)
- % reduction from baseline seizure frequency calculated
- Percentiles calculated for % reduction in seizure frequency at each dose
Comparison of gabapentin and pregabalin: Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Base (seizures/month)</td>
<td>14.0 (12.4, 15.6)</td>
</tr>
<tr>
<td>log Base (seizures/month)</td>
<td>-6.3 (5.9, 6.7)</td>
</tr>
<tr>
<td>Emax (maximal fractional change)</td>
<td>2.24 (0.20, 4.48)</td>
</tr>
<tr>
<td>Placebo (maximal fractional change)</td>
<td>-0.15 (-0.29, -0.009)</td>
</tr>
<tr>
<td>ED50 (mg)</td>
<td>463.0 (161.3, 964.7)</td>
</tr>
<tr>
<td>ProportionA</td>
<td>0.95 (0.93, 0.98)</td>
</tr>
</tbody>
</table>

Comparison of gabapentin and pregabalin

- A comparison of the dose-response relationship for gabapentin and pregabalin reveals that pregabalin was 2.5 times more potent, as measured by the dose that reduced seizure frequency by 50% (ED50).
- Pregabalin was more effective than gabapentin based on the magnitude of the reduction in seizure frequency (Emax)

Simulations of gabapentin and pregabalin

- Three hundred clinical trials for each drug were simulated conditioned on the original study designs.
- Each simulated trial was analyzed to estimate % median change in seizure frequency.
- The observed and model-predicted treatment effects of median reduction in seizure frequency for gabapentin and pregabalin are illustrated for all subjects and for responders.
- Data points represent median percentage change from baseline in seizure frequency for each treatment group (including placebo). The shaded area corresponds to predicted 10th and 90th percentiles for median change from baseline in seizure frequency.
Relationship Between %Change in Seizure Frequency (Relative to Baseline) and Daily Dosage of Gabapentin and Pregabalin

Clinical trial simulation (CTS):
- CTS provides a powerful and flexible tool to evaluate the performance of alternative designs, analysis strategies, and decision criteria, under a variety of assumptions about the anticipated data and trial conditions, incorporating the impact of the uncertainty in these assumptions.
CTS Procedure

Simulate \( \rho_i \sim N(3.27, 0.6^2) \)

Simulate Data \( Y_{ij} \mid \rho_i \sim N(\rho_i, 7.0^2) \) \( j=1, \ldots, n \)

Calculate Mean \( \bar{Y}_i = \frac{1}{n} \sum_{j=1}^{n} Y_{ij} \)

Repeat for \( i = 1, \ldots, N \) trials

Compare Truth vs Data-Analytic Decision

Apply Decision Rule: Go if \( \bar{Y}_i > \rho \)
No Go if \( \bar{Y}_i < \rho \)

Calculate Metrics 
\( P(\text{Go}) \)
\( P(\text{correct}) = P(\text{Go}) + P(\text{No Go}) \)

Mean Model Example

Results – \( n=100 \)

<table>
<thead>
<tr>
<th>Decision</th>
<th>No Go (( \bar{Y}_i &lt; 3 ))</th>
<th>Go (( \bar{Y}_i &gt; 3 ))</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta &lt; 3 )</td>
<td>2277</td>
<td>989</td>
<td>3266</td>
</tr>
<tr>
<td></td>
<td>22.77%</td>
<td>9.89%</td>
<td>32.66%</td>
</tr>
<tr>
<td>( \Delta \geq 3 )</td>
<td>1598</td>
<td>5136</td>
<td>6734</td>
</tr>
<tr>
<td></td>
<td>15.98%</td>
<td>51.36%</td>
<td>67.34%</td>
</tr>
<tr>
<td>Total</td>
<td>3875</td>
<td>6125</td>
<td>10,000</td>
</tr>
<tr>
<td></td>
<td>38.75%</td>
<td>61.25%</td>
<td>100%</td>
</tr>
</tbody>
</table>

\( P(\text{Go}) = 61.25\% \)
\( P(\text{correct}) = 22.77\% + 51.36\% = 74.13\% \)

Example: Type 2 diabetes

MAD Study Design Model-Based Evaluation

Clinical team wanted to do a short phase 1 study to estimate robustness to predict long-term outcome in type 2 diabetic patients.
Question

• Can a 2 wk or 4 wk MAD study in T2DM provide enough data to robustly predict the long-term, i.e. 16wk, efficacy and safety?
  — Fasting plasma glucose (FPG), HbA1c and risk of edema
• Early Go/No-go decision
• Guide dose-selection for PoC study

Prior in-house knowledge

• Rivoglitazone (PPARγ agonist)
• PK/PD model describing longitudinal relationship between Rivoglitazone exposure and FPG, HbA1c, and risk of edema

PK/PD model for FPG/HbA1c/Hb

Shashank et al, 2008, JCP
Predictive check for FPG
• Circles represent the observed data
• Lines represent 5, 50 and 95th percentile of the observed data.
• Shaded area represent 90% CI of model predicted 5, 50 and 95th percentile

Predictive check for HbA1c
• Circles represent the observed data
• Lines represent 5, 50 and 95th percentile of the observed data.
• Shaded area represent 90% CI of model predicted 5, 50 and 95th percentile

Flow diagram:
Original dataset
Subset 2 wk and 4 wk data
Estimate model prm using 2 wk data*
Estimate model prm using 4 wk data*
Estimate model prm using original data*
Trial simulation to obtain prediction at 16 wk
Trial simulation to obtain prediction at 16 wk
Trial simulation to obtain prediction at 16 wk
Summarize results
Compute probability of success
*: requires NONMEM run

*requires NONMEM run
Trial Design

- Study design
  - 20% treatment naïve
  - 42% female
  - Total 50 subjects
    - 5 cohorts of 10
    - 8 on treatment 0.5, 1, 2, 3, or 5mg, and 2 on placebo

Sampling schedule

- FPG
  - 2wk: daily from -14 to 24 days after first dose
  - 4wk: daily from -14 to 38 days after first dose
- HbA1c
  - 2wk: -14, predose, 7, 14, and 24 days after first dose
  - 4wk: -14, predose, 7, 14, 21, 28, and 38 days after first dose

Evaluation Methods

- Simulation of 100 trials
- Fit model to 2wk and 4wk simulated study data
- Predict 16wk CFB using estimates from the fitted model
- Calculate the bias and precision

\[
\text{% Relative root mean square error (RMSE)} = 100 \sqrt{\frac{\text{RMSE}_{\text{Simulated}}}{\text{RMSE}_{\text{Simulated-Predicted}}}}
\]
Prediction of FPG

Number of successful predictions (relative bias <20% and >-20%)

<table>
<thead>
<tr>
<th>Dose</th>
<th>2 wk study</th>
<th>4 wk study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td>1 mg</td>
<td>55</td>
<td>73</td>
</tr>
<tr>
<td>2 mg</td>
<td>48</td>
<td>81</td>
</tr>
<tr>
<td>3 mg</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>5 mg</td>
<td>57</td>
<td>77</td>
</tr>
</tbody>
</table>

RMSE%   44         28        26          27          26

Prediction of HbA1c

Number of successful predictions (relative bias <20% and >-20%)

<table>
<thead>
<tr>
<th>Dose</th>
<th>2 wk study</th>
<th>4 wk study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>1 mg</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>2 mg</td>
<td>46</td>
<td>50</td>
</tr>
<tr>
<td>3 mg</td>
<td>49</td>
<td>58</td>
</tr>
<tr>
<td>5 mg</td>
<td>53</td>
<td>61</td>
</tr>
</tbody>
</table>

RMSE%   384        37        24        25          25

Prediction of 16 wk FPG CFB

- Overall, the prediction of FPG is better than HbA1c.
- Response at higher dose is better predicted than lower dose.
- 4wk study is more predictive than 2wk study.

Prediction of 16 wk HbA1c CFB

- Response at higher dose is better predicted than lower dose.
- 4wk study is more predictive than 2wk study.
**FPG dose-response prediction**

**Criteria for success**

- Difference in FPG $\geq 10$ mg/dL is considered clinically significant.
- If all three model predicted FPG at placebo, 1 mg and 5 mg are only different from the corresponding true value less than 10 mg/dL, the model-based dose-response prediction is considered a useful prediction to guide the dose selection for PoC. Then the trial is considered a successful trial.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>2 wk study</th>
<th>4 wk study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>92</td>
</tr>
</tbody>
</table>

**Number of successful trials for dose-response prediction**

**FPG dose-response prediction**

Scenario 1 and Scenario 3 graphs show:
- Red line is true response.
- Dotted line is predicted response.

**HbA1c dose-response prediction**

**Criteria for success**

- Difference in HbA1c $\geq 0.3\%$ is considered clinically significant.
- If all three model predicted HbA1c at placebo, 1 mg and 5 mg are only different from the corresponding true values less than 0.3%, the model-based dose-response prediction is considered a useful prediction to guide the dose selection for PoC. Then the trial is considered a successful trial.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>2 wk study</th>
<th>4 wk study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>79</td>
</tr>
</tbody>
</table>

**Number of successful trials for dose-response prediction**
Conclusions of simulation

• The proposed study would not robustly predict 16wk CFB value with the typical number of subjects studied in an MAD (<=50) and truncated treatment period (<=4 wk).
• In general, a 4wk treatment study has higher prediction accuracy and precision than a 2wk treatment study, however, not markedly higher.
• Both 2wk and 4wk treatment study can provide valuable information to aid the dose selection for PoC study.
• Based on an empirical criteria, 4 wk treatment study is more robust than 2 wk treatment study to aid dose selection.

Final Remarks

• Optimizing trials based solely on conventional operating characteristics (e.g., power) may not always meet the needs of the organization
  – The organization wants to know how the compound is expected to perform in a given trial
  – Consider the routine calculation of P(success) and P(correct) in addition to power
• Routinely evaluate different QDCs, designs, model assumptions, and data-analytic methods when evaluating trial performance metrics
  – Generate contingency tables comparing data-analytic decisions to truth to understand false positive and false negative tradeoffs
Final Remarks

• Models provide a quantitative summary of our knowledge of the compound
  • For MBDD to be successful the models must be predictive
    • Routinely evaluate the predictive performance of the models as new data emerge
  • MBDD is a knowledge investment strategy
    • Time and resources are needed to extract as much information as we can from the data we generate
  • A process must be established for MBDD to realize its full potential
• Greater collaboration is needed
  • Statisticians, CP leads, pharmacometricians