Acknowledging Parameter Uncertainty in the Simulation-Based Design of an Actinomycin-D Pharmacokinetic Study in Pediatric Patients With Wilms’ Tumor or Rhabdomyosarcoma

John T. Mondick, Leonid Gibiansky, Marc R. Gastonguay, Gareth J. Veal, Jeffrey S. Barrett

Division of Clinical Pharmacology & Therapeutics

The Children’s Hospital of Philadelphia®

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Actinomycin-D

Background

• Wilms’ tumor, Rhabdomyosarcoma
• Clinical use > 40 years
• No PK information to guide dosing
• Dosing regimens modified to minimize toxicity (VOD, myelosuppression)
• Toxicity rates in children < 1 year double
• Dosing modifications < 1 year
• Open label trial of actinomycin-D (AMD) in children with Wilms’ Tumor or Rhabdomyosarcoma proposed
• Examine AMD PK properties with the goal of providing dosing guidance
• Need to understand Dose → Exposure in children < 1 year old
• Incorporate uncertainty in the parameter estimates via probability density functions
• Uncertainty in parameters implemented as inter-trial variability

R/NONMEM Toolbox for Simulation from Posterior Parameter (Uncertainty) Distributions - Gibiansky

NMSUDS: R/NONMEM® Toolbox for Simulations from Uncertainty Distributions
1. Construct Pop PK model to describe AMD disposition in children

2. Perform clinical trial simulations incorporating parameter uncertainty for the design and evaluation of a prospective large-scale AMD trial in pediatric cancer patients, and subsequent sensitivity analysis

3. Power the study to be able to accurately and precisely estimate clearance for children < 1 year
Model Characteristics

- Developed from PK data in 33 children, ages 1.5 to 20 years
- Nonlinear mixed-effects modeling with NONMEM
- 3 compartment, allometric scaling
- Log-transformed parameters
- THETA prior distribution – NONMEM variance/covariance matrix (multivariate normal)
- OMEGA prior distribution – mode, df (inverse Wishart)
Simulations With Uncertainty

Procedure

1. Create NMTRAN template data file Simulation of 500 sets of unbiased parameters from the population posterior distributions
2. Simulation 500 replicate PK data sets
3. Reference model fit to PK data
4. Parameter estimates and model diagnostic information collected
5. Bias and precision calculated
6. Global sensitivity analysis
7. Study design refinement
8. Repeat process until informative design identified
Methods

Study Design Assessment

- Feasibility of study design
- Ability to accurately estimate V1, CL
- Bias +/- 20%, no trends over range of unbiased parameters
- Powered accurately estimate clearance for children < 1 year
n=200

Group 1:

• 5 to 15 minutes
• 0.75 to 1.5 hours
• 3.5 to 4.5 hours
• 48 - 96 hours (n=50)

Group 2:

• 15 to 30 minutes
• 2 to 3 hours
• 5 to 6 hours
• 48 - 96 hours (n=50)
Results

Initial Design

![Graph showing the relationship between bias (%) and CL (L/h) on the left and V1 (L) on the right. The graphs display a scatter plot with a trend line indicating a negative correlation.](image-url)
Results

Initial Design

![Graph showing bias (%) for different categories: V1, V2, V3, CL, Q2, Q3, OMV1, OMCL. The x-axis represents the categories, and the y-axis shows the bias in percentage. The graph includes error bars and a box plot.]
1. 24 hour sample added in 50% of patients
2. A rich sampling schedule was examined to evaluate the proposed sampling windows
3. Patients with a sample collected 48 – 96 hours increased to 50%
4. Sample fixed at 5 minutes included for both schedules
5. Sampling windows adjusted for remaining times
n=200

• Group 1:
  • 5 minutes fixed
  • 10 minutes fixed
  • 2 - 3 hours
  • 24 - 28 hours (n=100)
  • 48 - 96 hours (n=100)

• Group 2:
  • 5 minutes fixed
  • 0.75 - 1.5 hours
  • 5 - 6 hours
  • 24 - 28 hours (n=100)
  • 48 - 96 hours (n=100)
Results
Final Study Design

![Graph showing bias (%)](image-url)

- **CL (L/h)**
  - -20
  - -10
  - 0
  - 10

- **V1 (L)**
  - -40
  - -20
  - 0
  - 20
  - 40
  - 60
Results

Final Study Design

![Graph showing bias (%)]
Age Effect

• Age effect on CL added to model

\[ \text{AEFF} = 0 \]

\[ \text{IF(AGE.LE.1) THEN} \]

\[ \text{AEFF} = \text{THETA}(7) \]

\[ \text{ENDIF} \]

\[ \text{TVCL} = \text{THETA}(4) + 0.75 \times \log(WT/70) + \text{AEFF} \times \log(\text{AGE}) \]

\[ \text{LCL} = \text{TVCL} + \text{ETA}(2) \]

\[ \text{CL} = \exp(\text{LCL}) \]

• 500 values for AEFF drawn from RUNIF between 0 and 0.5
Age Effect

Power Analysis

![Graph showing the relationship between n per group and ΔCL (L/h) for different power levels (70%, 80%, 90%) with data points and lines indicating the power analysis results.](image.png)
Conclusions

• A feasible and informative trial design was identified for an AMD clinical trial in pediatric patients with Wilms’ tumor or Rhabdomyosarcoma

• Design was modified to be robust across the uncertainty in key parameters
Conclusions

• Appropriately powered to capture potential clearance differences in children < 1 year

• Results of this effort have been incorporated into a prospective trial protocol to be conducted through the Children’s Oncology Group Phase I Consortium