PHARM 609: ADVANCED PHARMACOKINETICS

Winter, 2016.

Assignment #3: Non-Linear Mixed Effects Models

Instructor: Dasha Hajducek.

Due date: April 22, 2016 by midnight.

Please submit the solutions in PDF form via email to cdmariac@uwaterloo.ca.

Deliverables:

1. Report of the pharmacokinetic analysis.
2. Phoenix project file (*.phxproj).

Data set:

Available on LEARN with name CIPROFLOXACIN.csv.

Variables:

ID: subject identification number.
DV: Concentration, mg/L.
TIME: time of dose or concentration, h.
AMT: dose amount, mg/kg
RATE: rate of infusion, mg/h/Kg
WT: body weight, kg.
AGE: age, years.
GEND: 1=Male, 2=Female.

Study name:

Ciprofloxacin pharmacokinetics in pediatric patients.

Study design:

Pediatric patients between the ages of 3 months and 5 years were treated for severe sepsis. Patients received ciprofloxacin by 1 hour intravenous infusion at a dose of 10 mg/kg twice daily for 7 to 14 days. Pharmacokinetic data were obtained from 20 patients. Patients provided serial blood samples on the 1st, 3rd and 8th days.

Objective:

To estimate typical population pharmacokinetic parameters for ciprofloxacin in pediatric patients and identify demographic factors as significant predictors of variability. 人口统计

Suggested Outline:

I. Description of the sample.

This section must include:

- Descriptive analysis of the concentration profiles, potential collinearity and demographic characteristics in the sample.
- Information on outliers and whether they were discarded from the analysis.

II. Model Selection

Important note: Ignore Phoenix warning messages of the type:
"In secondary parameter 'VSS' : depends on A1InfDose. Only initial value for last subject will be used."

i. Selection of the base model.

- One compartment IV structural model with infusion and exponential random effects.
  Mathematical form of the structural model:

$$C(t) = \frac{Dose}{CL_i \cdot t_i}\left\{1 - \exp\left(-\frac{CL_i}{V_i}t_i\right)\right\}\exp\left(-\frac{CL_i}{V_i}(t - t_i)\right)$$

- In Phoenix:
  - Select the *Set WNL* option in the *Structure tab*, select the *1cp infus* option and check the "*CL/V*" box.
  - Map the *RATE* variable to the *A1 Rate* heading.

This section must include:

- For each residual variance model explored (three at most):
    a. The mathematical expression of the base model, including the distributional assumptions involved.
    b. Evidence of the choice on diagonal or unstructured variance-covariance matrix of the random effects.
    c. Preliminary assessment of the effect of covariates on the response.
- Careful interpretation and any additional information (tables, plots) to support your choice.

ii. Selection of the covariate model.

For reference on parameterization of the weight variable, consult the attached research paper by Jian Wang et al. (2015).

This section must include:

- For each covariate functional relationship explored:
    a. The mathematical expression of the covariate model, including the distributional assumptions involved.
    b. The order of inclusion of covariates, as well as relevant statistical plots and measures.
- Careful interpretation and any additional information (tables, plots) to support your choice.
- Interpretation of the meaning of the estimated covariate coefficients and variance components.

III. Bootstrap Estimation

This section must include:

- Bootstrap results from the final model selected.
- Comparison in percent change of Bootstrap vs. Maximum Likelihood precision estimates. If they are very different, state the possible reasons of why this may be the case.

IV. Summary and conclusions

Any additional comments on the data, sample size, limitations of the selected model, outliers, modeling process and results.

V. Appendix

Include R codes used throughout the analysis, please refer to the sections for which the code was implemented.