A New Approach for Population Pharmacokinetic Data Analysis Under Noncompliance

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INTRODUCTION

- Multiple dose regimens are required to maintain drug concentrations in a therapeutic range for chronic diseases
- Non-compliance (omission/lack of adherence) to the prescribed regimen is a common problem in outpatient clinical studies
- Presence of non-compliance impacts meaningful data interpretation

PURPOSE

Evaluate an alternative method for analyzing outpatient PK data in the presence of noncompliance to the prescribed dosage regimen.

Multiple-dose PK Data Analysis

- After a single oral dose

$$SDF = B(e^{-ket} - e^{-kat})$$

where

$$B = \frac{FDka}{V(ka - ke)}$$

- After n oral doses

$$A = SDF + B[e^{-ket}\sum_{i=1}^{n-1} e^{-ke\cdot i\cdot\tau} - e^{-kat}\sum_{i=1}^{n-1} e^{-ka\cdot i\cdot\tau}]$$

A is the drug in the central compartment, SDF is the function that describes drug disposition after a single dose ka and ke are the absorption and elimination rate constants, respectively, τ is the dosing interval, n is the number of doses

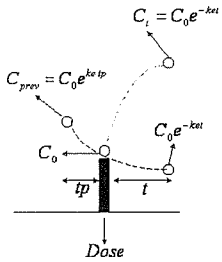
Conventional Method

- Complete dosing history or steady state assumption is required to model drug accumulation

$$A = SDF + B[e^{-ket}\frac{1-e^{-(n-1)\cdot ke\cdot\tau}}{1-e^{-ke\cdot\tau}} - e^{-kat}\frac{1-e^{-(n-1)\cdot ka\cdot\tau}}{1-e^{-ka\cdot\tau}}]$$

- Presence of noncompliance: equivalent to using wrong model for analysis

Alternative Method



C_{prev} : Pre-dose concentration
C_t : Post-dose concentration
t_p : Time elapsed between pre-dose sample and dosing
t : Time elapsed between dosing and post-dose sample
C_0 : Concentration at the time of dosing – scaling parameter

- When ka>ke and time is in the post-absorption/elimination phase

$$A = SDF + B[e^{-ket}\sum_{i=1}^{n-1} e^{-ke\cdot i\cdot\tau}] = SDF + B^*(e^{-ket})$$

- where, B* is a function of ke
- Ignoring ke component in B*

$$C = SDF + C_0(e^{-ket})$$

- C_0 is a scaling parameter

C_0 is modeled as an individual-specific parameter

$$C_{0ij} = C_0e^{\eta_i}$$

Observations are tied to known dosing time

$$C_{ij} = [C_{0i}e^{-ke_it} + B_i(e^{-ke_it} - e^{-ka_it})]e^{\varepsilon_{ij}}$$

ke estimation is not a function of imputed dosing history / recall times

METHODS

Simulation Details

- Number of subjects= 40
- Number of simulations=100
- V= 1L, CL= 0.693 L/hr, ($t_{1/2}$=1 hr), ka= 4 hr^{-1}, Dose= 10
- CV for IIV: CL (30%), V (30%), ka (30%)
- CV for RV: 10%
- Dosing times: 0, $3t_{1/2}$, $4t_{1/2}$, $5t_{1/2}$, $6t_{1/2}$, $7t_{1/2}$, $8t_{1/2}$, and $9t_{1/2}$ (in- patient dose)
- Sampling times: 15 min pre-dose (in-patient), 6, 21, 60 and 180 min post-dose
- Sampling times generated from a uniform distribution around the target times
- Simulation and estimation (FOCE) performed using NONMEM VI
- Noncompliance introduced by missed doses (omission)

  X_n= {(0,r),(1,1-r)}; X_n is the indicator for dose taken at the nth time (n≠ known dose)

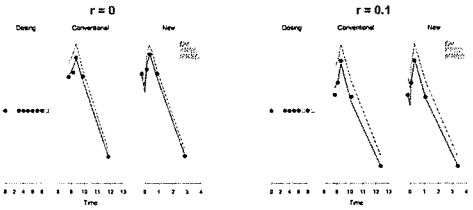
  Three cases: r=0%, r=10%, r=20%
- Data simulated under missed dose scenarios and analyzed using the conventional approach assuming full compliance
- Simulated data analyzed using the alternative approach
- Performance Measures

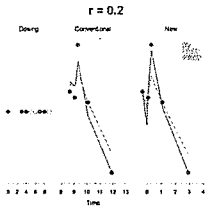
  Bias (me %) = mean [(est_i – tr_i)*100/tr_i]

  Imprecision (mae %) = mean [abs (est_i – tr_i)*100/tr_i]

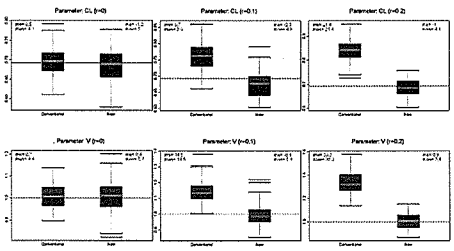
RESULTS

Representative PK Profiles

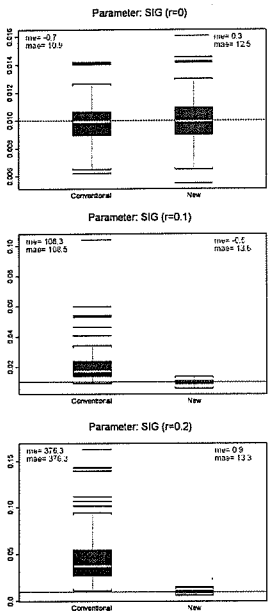




Structural Parameter Estimates



Residual Intraindividual Variability



CONCLUSIONS

- Biased and imprecise parameter estimates were obtained with the conventional approach in the presence of dose omission
- Bias and imprecision increased with the increase in non-compliance
- The biggest impact was observed on the estimate of residual intraindividual variability
- The new method was relatively robust and consistent in parameter estimation regardless of the degree of non-compliance

DISCUSSION

- The new method is an attractive alternative to analyzing outpatient data
- No assumptions/imputations for dosing history are required
- Decreased bias (especially in residual variability) can facilitate covariate analysis
- Decreased bias can allow reconciliation with Ph I data and/or data from different dosing regimens
- This approach is only applicable to:
  - -drugs with linear PK
  - -drugs exhibiting rapid absorption relative to elimination (ka>>ke)
  - -a certain study design

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