

Evaluation of an Alternative Approach for Multiple-Dose Population Pharmacokinetic Data Analysis in the Presence of Noncompliance

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INTRODUCTION

Noncompliance to the prescribed dosage regimen presents a challenge for population PK data analysis in outpatient studies.

Ignoring dose omission or making uninformed assumptions about patient drug intake history can compromise the objectives of the analysis and impact interpretation of exposure-response relationship.

PURPOSE

Evaluate a promising 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

$$SDF = B(e^{-ka} - e^{-kt})$$

$$\text{where, } B = \frac{FDka}{V(k_a - k_e)}$$

After n oral doses

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

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 a steady state assumption is required to model drug concentration/accumulation

$$C = SDF + B \left[\frac{e^{-ka} (1 - e^{-n \cdot ka \cdot \tau})}{1 - e^{-ka \cdot \tau}} - \frac{e^{-ka} (1 - e^{-n \cdot ka \cdot \tau})}{1 - e^{-ka \cdot \tau}} \right]$$

Presence of noncompliance: equivalent to using misspecified model for analysis

Alternative Method

$$C_i - C_{i-1} e^{-kt} + SDF$$



When $ka \gg ke$ and sample is in the post-absorption/elimination phase

$$A = SDF + B \left[e^{-ka} \sum_{i=1}^{n-1} e^{-ka \cdot i \cdot \tau} \right] = SDF + B \cdot (e^{-ka \cdot \tau})$$

where, B* is a function of ke

Ignoring the ke component in B*

$$C_i = SDF + C_0 (e^{-ka \cdot \tau})$$

C₀ is a scaling parameter

C₀ is modeled as an individual-specific parameter

$$C_0 = C_0 e^{\beta}$$

Observations are tied to known dosing time

$$C_i = \{SDF_i + C_0 e^{-ka \cdot \tau}\} e^{e^{\beta}}$$

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

METHODS

Simulation Details

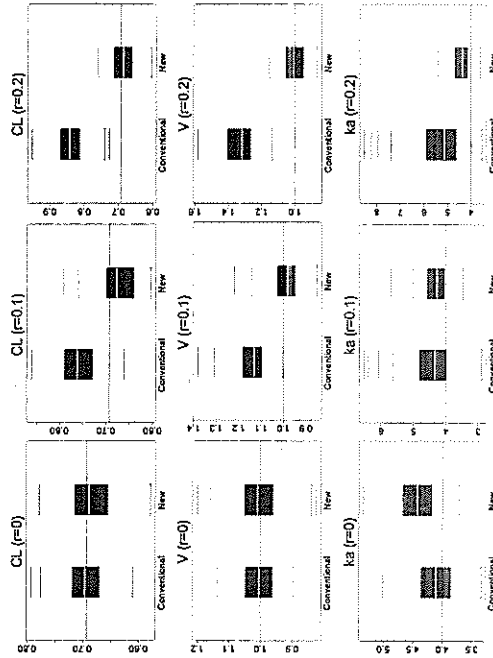
- Number of subjects= 40, number of simulations=100
- V= 1L, CL= 0.693 L/hr, (t_{1/2}=1 hr), ka= 4 hr⁻¹, Dose= 10
- CV for IV: CL (30%), V (30%), ka (30%); CV for RV: 10%
- Dosing times: 0, 3t_{1/2}, 4t_{1/2}, 5t_{1/2}, 6t_{1/2}, 7t_{1/2}, 8t_{1/2}, 9t_{1/2} (in-patient dose)
- Sampling times: 15 min pre-dose (in-patient), 6, 21, 60 and 180 min post-dose; generated from a uniform distribution around the target times
- Noncompliance introduced by missed doses (omission)
 $X_n = \{(0, \tau), (1, \tau)\}$; indicator for dose taken at the nth time (n≠ known dose)
 Three cases: r=0%, r=10%, r=20%
- Data analyzed using the conventional approach assuming full compliance and 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]
- Simulation and estimation (FOCE) performed using NONMEM VI

STUDY II

- Number of subjects= 40, number of simulations=250
- Noncompliance, r=0%, 0.2%, 0.3%
- CL equally divided by gender: CL_f = TVCL_f * (1 + DEL * GEN)_f^{0.75}; TVCL_f is the typical value in females (GEN=0), DEL is the fractional increment in males (GEN=1)
- Empirical distribution of ΔOFV constructed from analyzing data with and without the covariate under H₀: 95th percentile yielded the cutoff for Type I error
- Data simulated under H₁ and analyzed with and without the covariate; fraction of runs with ΔOFV > cutoff, yielded the power

RESULTS

Structural Parameter Estimates



Residual Intraindividual Variability



Covariate Selection

Scenario	Method	Power (%)	Cutoff
r = 0	Conventional	82	3.61
	New	74	3.83
r = 0.2	Conventional	57	3.73
	New	68	4.13
r = 0.3	Conventional	44	4.77
	New	64	4.17

CONCLUSIONS

- Biased and imprecise parameter estimates, which became progressively worse with dose omission, were obtained with the conventional approach
- Residual variability registered the biggest impact of noncompliance
- The new method was relatively robust and consistent in parameter estimation regardless of the degree of noncompliance
- The two methods differed with respect to Type I error and the power for covariate detection
- An inflated Type I error and reduced power was observed for the conventional method under noncompliance

DISCUSSION

- Uncertain dosing histories in outpatient studies make the new method an attractive alternative for data analysis since no assumptions/imputations are required.
- Decreased bias (especially in residual variability) can facilitate covariate analysis and reconciliation with Ph I data and/or data from different dosing regimens.
- The method affords robustness in parameter estimation, type I error rate and power for covariate detection
- This method is only applicable to:
 - a) drugs with linear PK
 - b) drugs with rapid absorption relative to elimination ($ka \gg ke$)
 - c) a specific study design i.e. in-patient dosing with sufficient sampling
- This approach will be further developed with respect to designing sampling schemes utilizing optimal design, multi compartment disposition characteristics and multiple PK occasions.