
Problematic Estimation of K_a Using Peak-Trough Sampling Schemes

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Part I:

Introduction

Introduction

- **Population analysis using nonlinear mixed effects models is a commonly used tool to analyze sparse data**
- **The precision and bias of the estimated parameter values are, in general, influenced by:**
 - ◆ **Number of patients**
 - ◆ **Number of samples per patient**
 - ◆ **Sample collection times**

Selection of Sampling Times

- **Requires prior knowledge about the model which will be used to describe the pharmacokinetics of the drug**
- **The number of samples/patient and the timing of the samples will depend on which parameters are of interest**
- **Multiple samples must be collected for each patient to separate IIV and RV**

Peak-Trough Sampling Scheme For Orally Administered Drugs

- **Involves the collection of two samples:**
 - ◆ **“Peak”** : ~ T_{max} from full-profile data
 - ◆ **“Trough”** : ~End of the dosing interval
- **Peak samples provide information relative to the estimation of K_a and V**
- **Trough samples provide information relative to the estimation of CL and V**

Reasons for Not Sampling During the Absorption Phase:

- **In purely observational studies, the collection of additional samples to characterize absorption may be of no benefit to the patient**
- **For studies in which interest is not on defining absorption, investigators for practical reasons choose to ignore this process**
- **Variability in the time of peak sample collection may allow for a reasonable estimate of K_a**

End Result of Non-Informative Data During the Absorption Phase:

- **Ka often is not reliably estimated and may need to be fixed based upon the best available *a priori* information**
 - ◆ **Computer fitting**
 - ◆ **Area-function (IV and PO data)**
 - ◆ **Wagner-Nelson (1-CMT, PO data)**
 - ◆ **Loo-Riegelman (2+ CMT, PO data)**
- **Little consideration is given to the effect of possible misspecification of Ka on the other parameters in the model (e.g., CL and V)**

Consequences of Misspecifying K_a

“Effect of Misspecification of the Absorption Process on Subsequent Parameter Estimation in Population Analysis”

(JR Wade et al., *J Pharmacokin. Biopharm.* 21:209-222, 1993)

(Wade *et al.*)

Methods:

- **Sparse datasets were simulated using 1-CMT oral steady-state models differing in:**
 - ◆ **Sampling times**
 - ◆ **Absorption rates & IIV**
 - ◆ **Input functions (first- vs. zero-order)**
- **A 1-CMT model w/first-order absorption and elimination was then fit to each dataset**

(Wade *et al.*)

Key Findings

- **No data in the absorption phase**
 - ◆ **CL and V were insensitive to K_a**
- **Non-informative data in the absorption phase**
 - ◆ **Only V was sensitive to K_a**
 - ◆ **Inclusion of IIV on K_a increased the magnitude of IIV on V, rather than RV**
- **Use of the incorrect model for drug input did not influence CL and V estimation**

Part II: Recent Experience

Phase II Data For Orally Administered Drug X

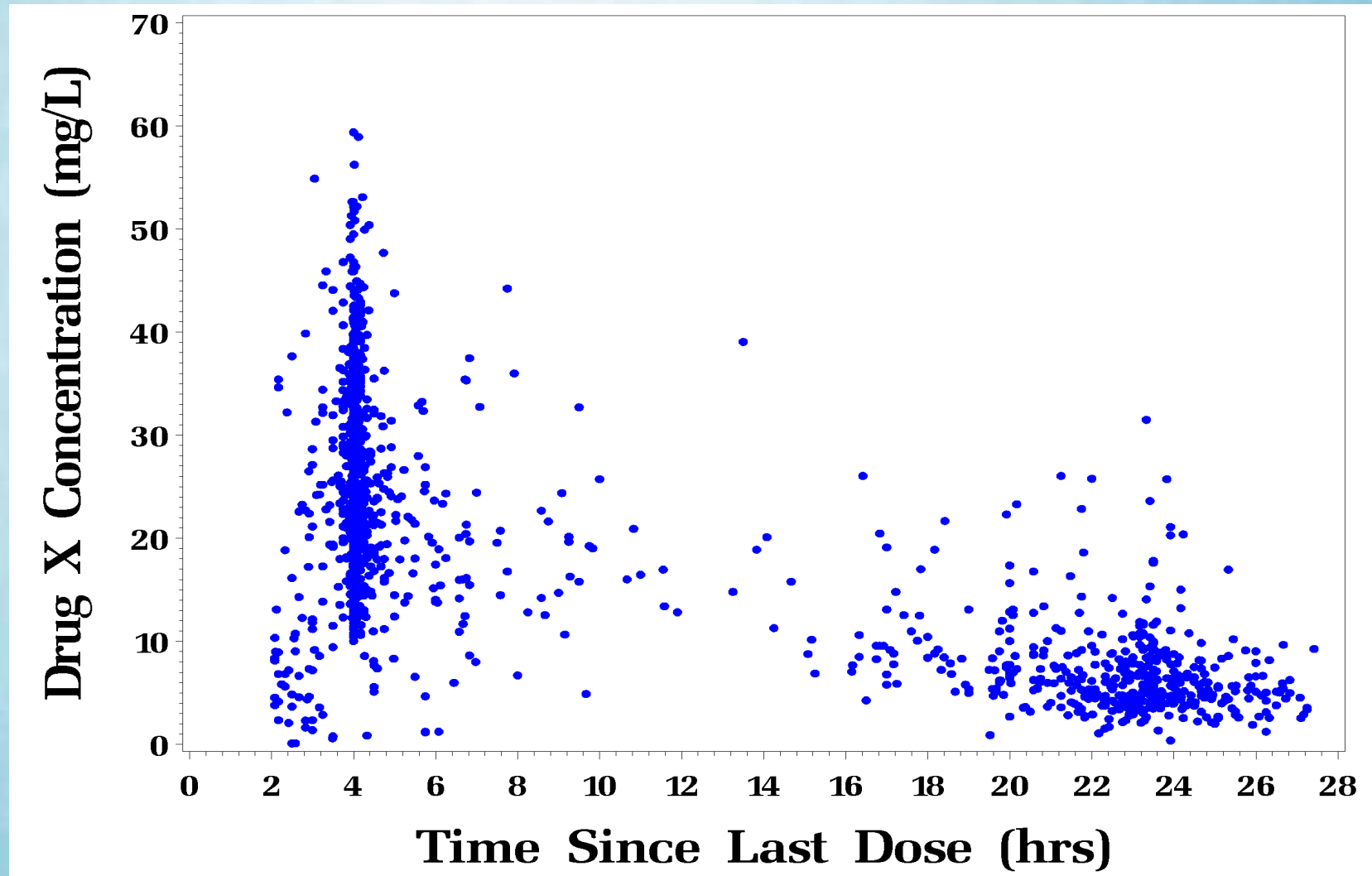
Background

- **Rapid absorption ($T_{max} \sim 4$ hr)**
- **Eliminated by excretory and metabolic pathways ($T_{1/2} \sim 14$ hr)**
- **Full profile Phase I data out to 72 hr was characterized using a 1-CMT model with first-order absorption and elimination**
 - ◆ **Exponential IIV on CL, V and K_a**
 - ◆ **Proportional RV**

Study Design

- **Dosing Scheme:**
 - ◆ **QD for 3 Days**
- **Sampling Scheme:**
 - ◆ **Day 1: Pre-dose and Peak**
 - ◆ **Day 3: Peak and Trough**

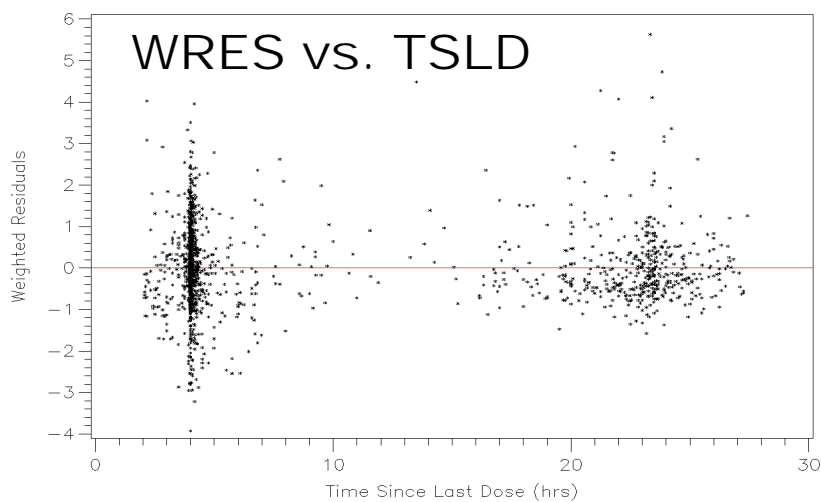
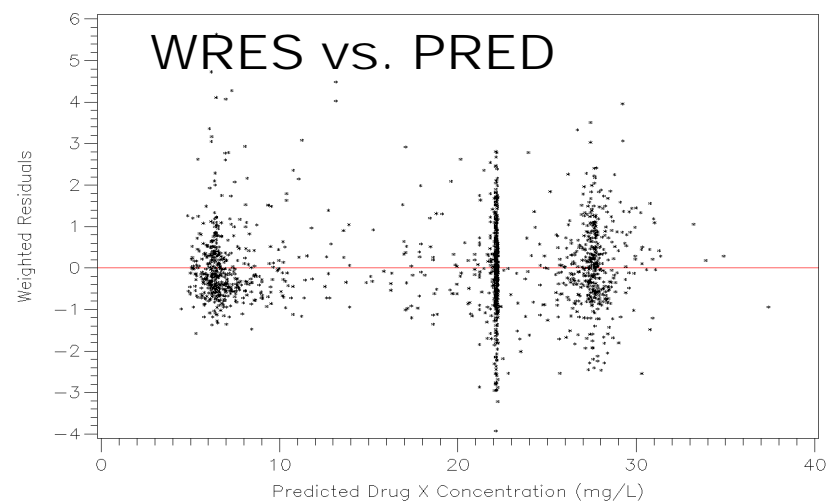
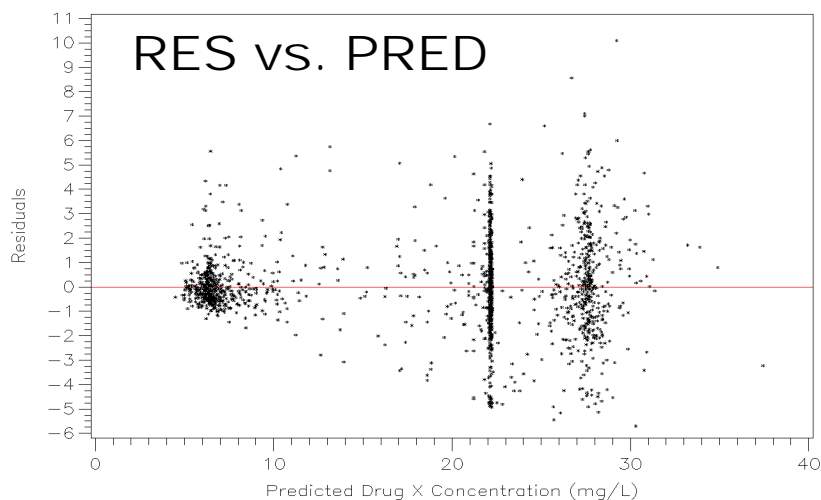
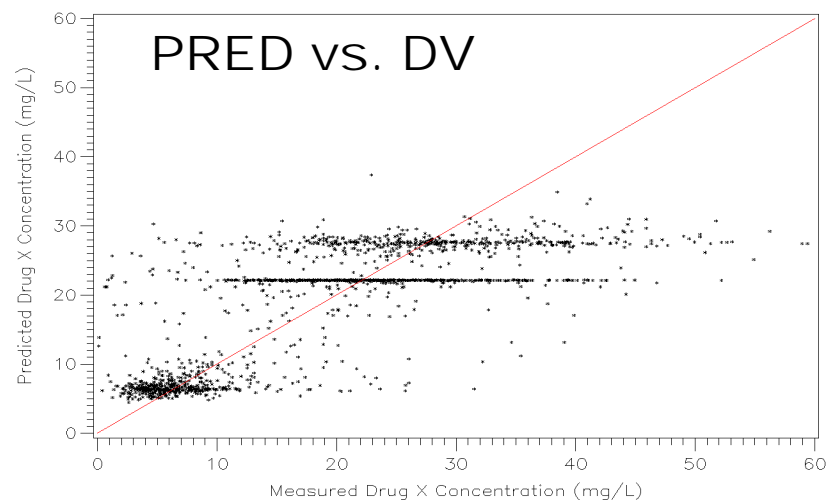
Observed Concentration-Time Data



Base Structural Model

- **1-CMT model with first-order absorption and elimination was fit to the sparse data out to ~24 hr**
 - ◆ **Exponential IIV on CL, V, Ka**
 - ◆ **Proportional RV**
- **Model was assessed for “goodness of fit”**
 - ◆ **Evaluation of parameter estimates**
 - ◆ **Diagnostic plots**

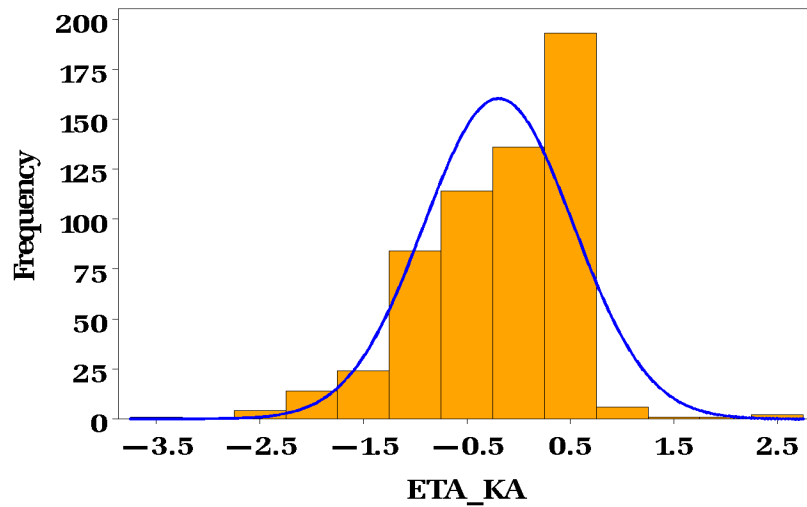
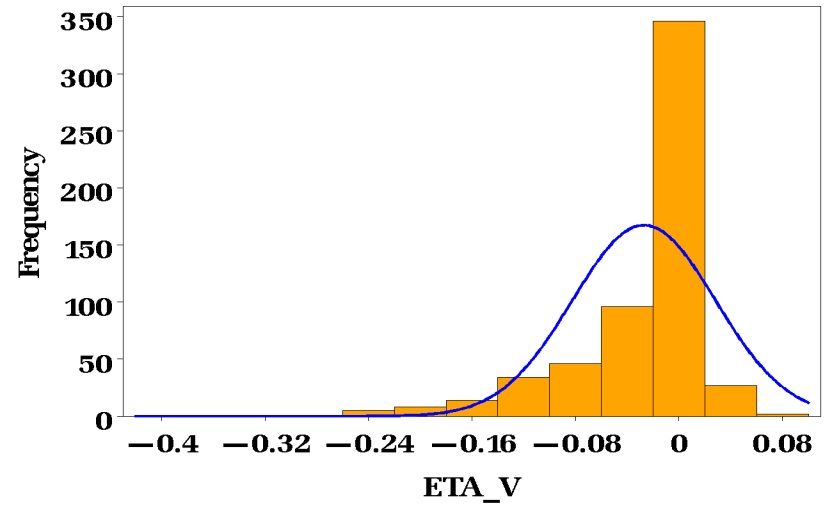
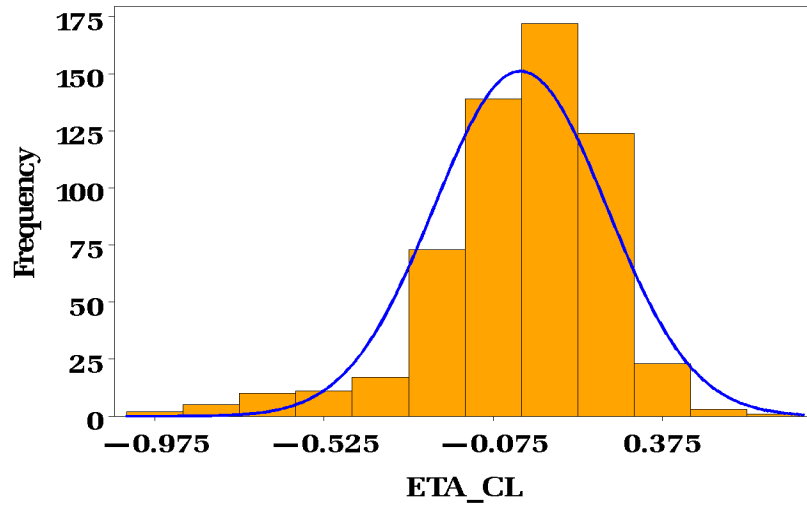
Goodness of Fit Plots



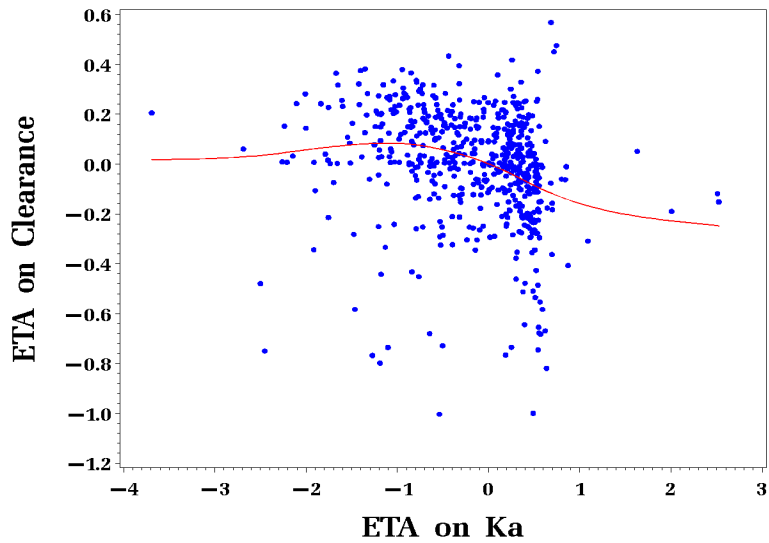
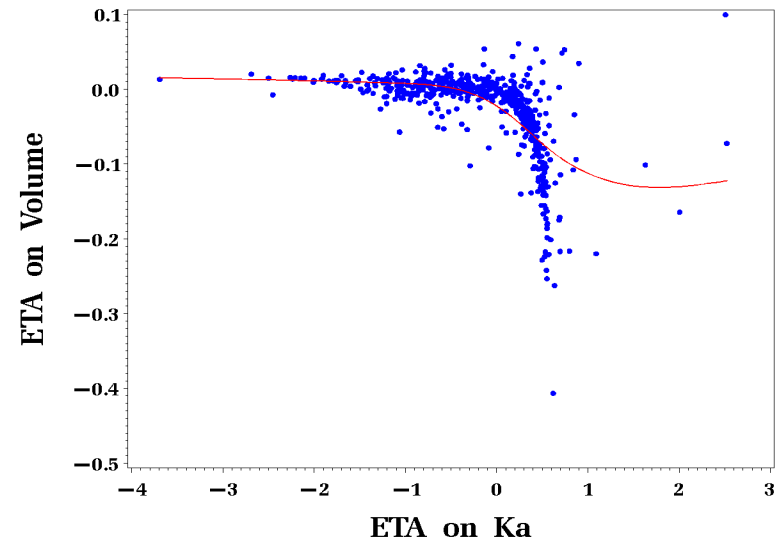
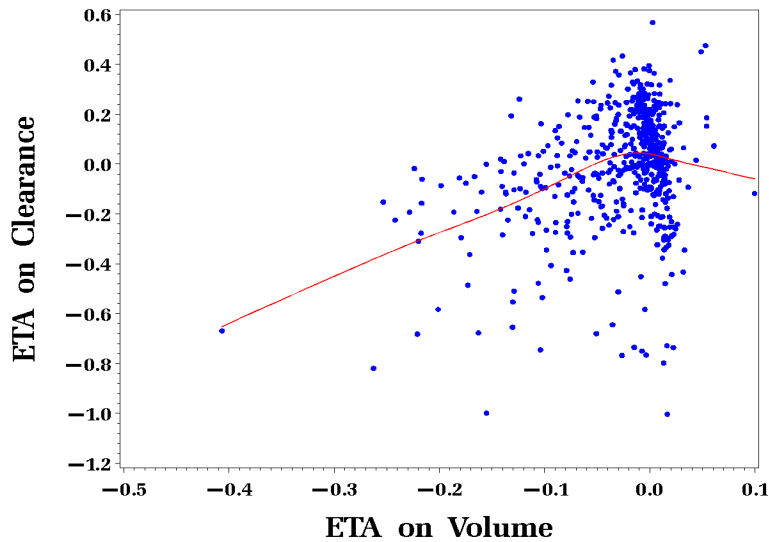
Parameter Estimation

Parameter	Population Mean Estimate	%SEM
Ka (1/hr)	1.5	13
CL (mL/min)	70	5
V (L)	50	4
IIV on Ka (%CV)	147	30
IIV on CL (%CV)	33	15
IIV on V (%CV)	14	170
RV (%CV)	29	13

Eta Distributions



Eta Biplots



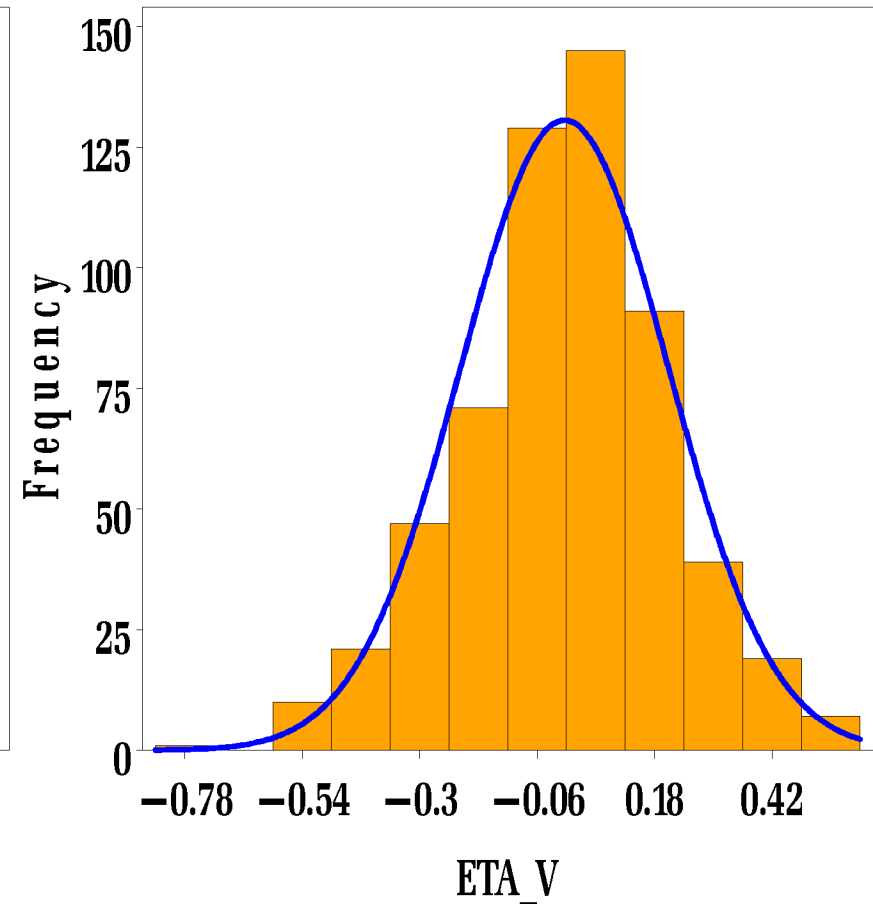
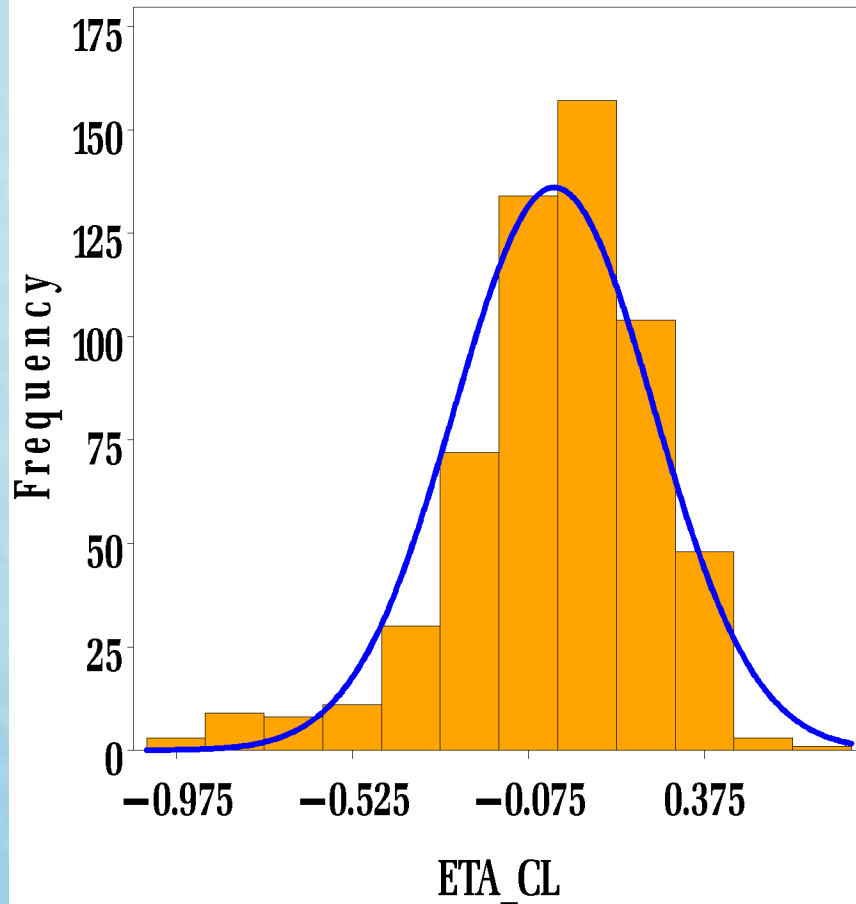
Base Structural Model

- **1-CMT model with first-order absorption and elimination was fit to the sparse data out to ~24 hr**
 - ◆ **Exponential IIV on CL and V**
 - ◆ **Proportional RV**
- **Model was re-assessed for “goodness of fit”**

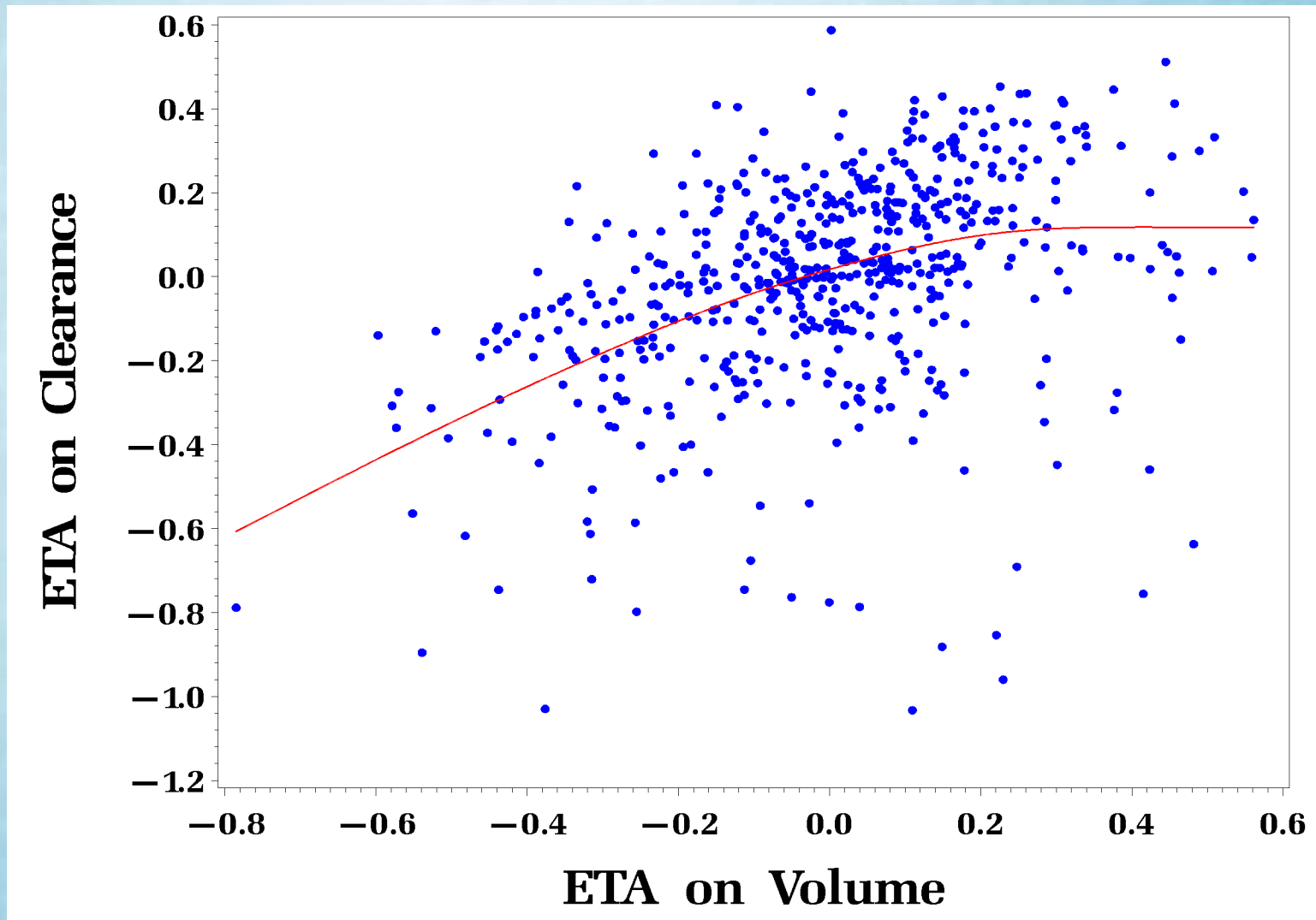
Parameter Estimates: Removed IIV on Ka

Parameter	Population Mean Estimate	%SEM
Ka (1/hr)	2.5	34
CL (mL/min)	70	2
V (L)	50	2
IIV on CL (%CV)	36	15
IIV on V (%CV)	32	17
RV (%CV)	27	13

Eta Distributions: Removed IIV on Ka



Eta Biplot



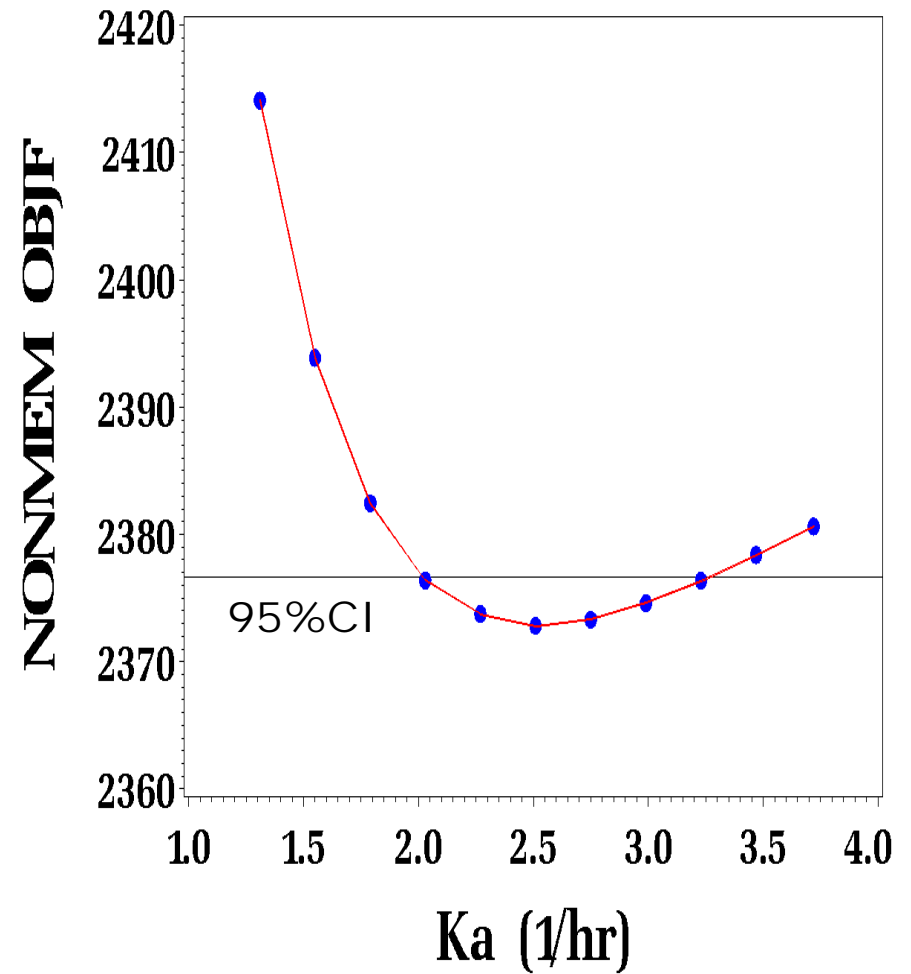
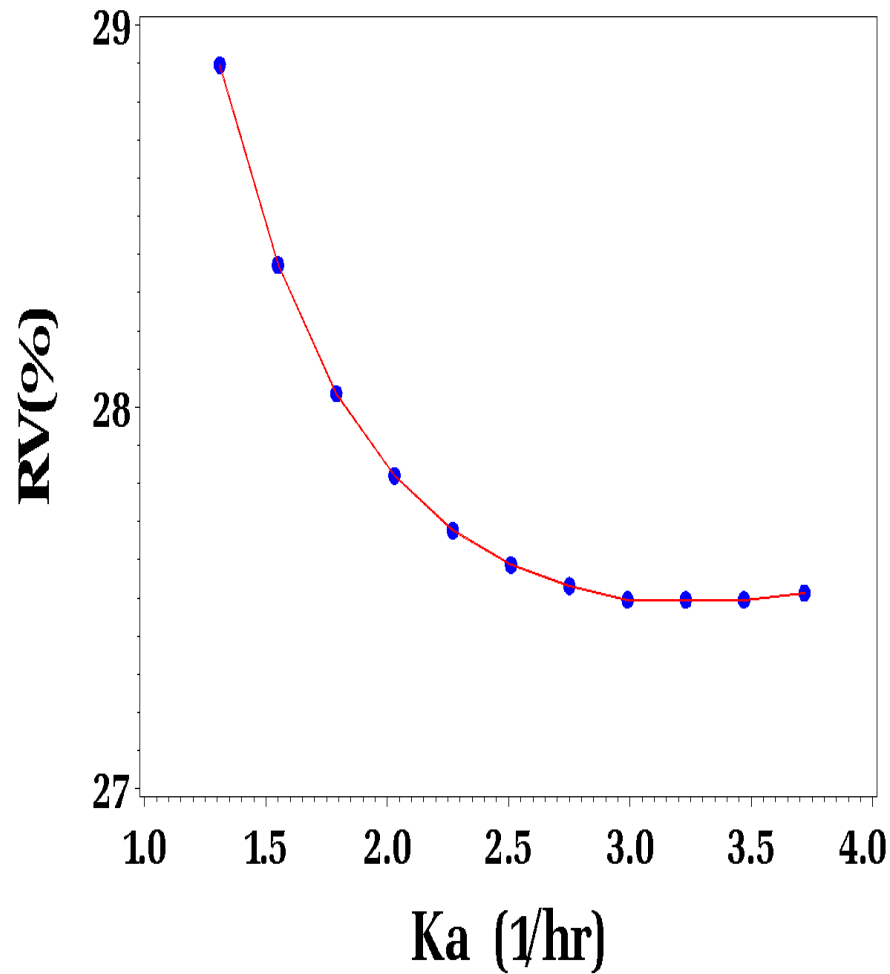
Base Structural Model

- **NONMEM could not distinguish between IIV in KA and V, which may be a result of not having enough data in the absorption phase**
- **Variability may have been assigned to Ka or V based upon the timing of the peak sample collection**
- **Removal of the IIV on Ka resulted in a reasonable estimate for the IIV on V prior to the evaluation of covariates**

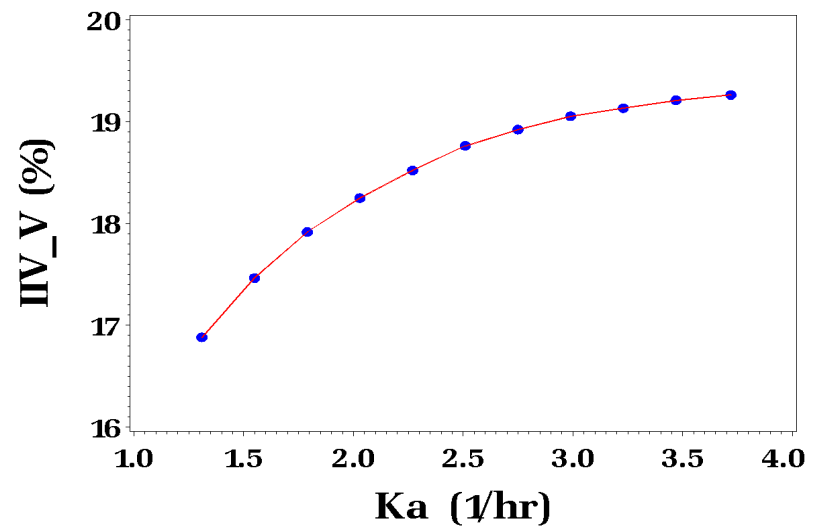
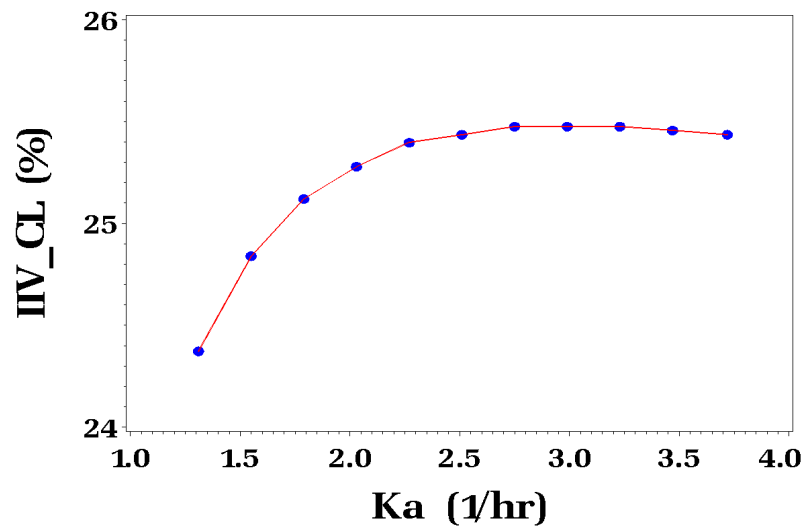
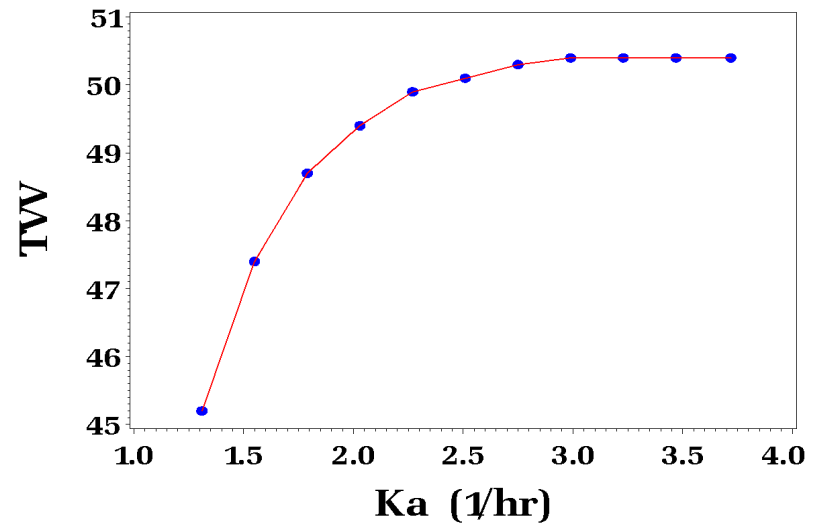
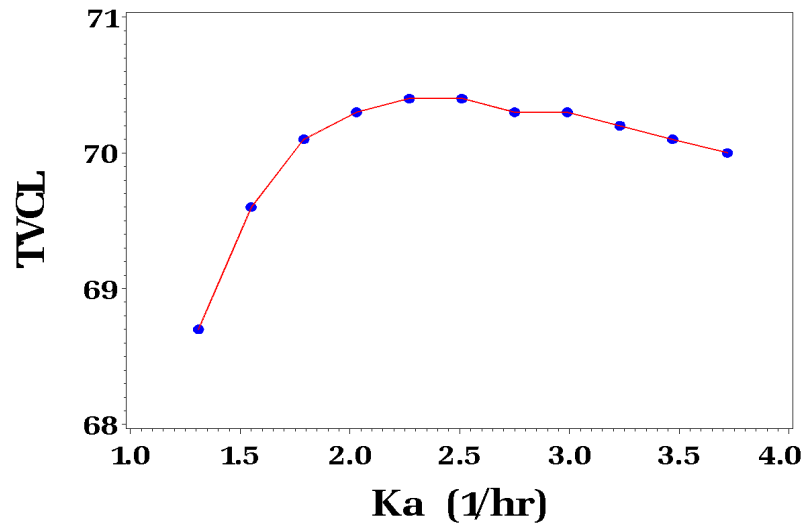
Sensitivity Analysis

- **The sensitivity of the other model parameters to the estimate of Ka was evaluated**
 - ◆ **Ka was fixed to values $\pm 50\%$ in 10% increments, and the resulting parameter estimates were evaluated**
 - ◆ **The components of the structural model were then mapped over the range of fixed Ka values selected**

Sensitivity Analysis



Sensitivity Analysis (cont.)



Summary

- **Make sure the estimate of K_a is reliable**
- **Consider performing “sensitivity analyses” if a parameter is fixed or if there may not enough data to support model parameters**
- **This example shows the need to implement sparse sampling strategies that provide informative data**
 - ◆ **Less restrictive definitions for peak times**
 - ◆ **Use of time windows**



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Acknowledgements

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