MPI-103

Uniqueness of Solutions to Compartmental Models of Population Pharmacokinetics for Drugs Undergoing Complex Metabolism

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ABSTRACT

Purpose. To investigate parameter identifiability and uniqueness of solutions to compartmental population pharmacokinetic (PPK) models for drugs with complex metabolism.

Methods. As a solution to parameter identifiability, fixing volume of distribution (VOD) of a parent drug (P) or its metabolites has been extensively reported during PPK model development when neither excretion data for each species were available nor metabolite doses were separately administered. A hypothetical P and its metabolites (M1 and M2) with a metabolic pathway P → M1 ↔ M2 was used to simulate the development of a 5-compartment PPK model (2 for P, 1 for M1 and 2 for M2) in NONMEM® and 1200 PK samples from 240 patients for P, M1, and M2 were collected at 0, 1, 2, 4, and 24 hrs after an IV infusion (90 min) of 200 mg P. Elimination characteristics of the drug were assumedly known from prior metabolism/mass balance studies.

Results. The solution to the mass balance differential equations in this PPK model was not unique. The PPK model fit all concentration profiles equally well when the VOD of P, M1, and/or M2 was fixed at different values, and the PK parameter estimates (PE) were either unreasonable or misleading depending on the value at which VOD was fixed. When elimination characteristics were used as boundary conditions through clearances to the model, the obtained PK parameter estimates were unique and interpretable.

Conclusion. Elimination characteristics, rather than VOD, assumed or available from prior studies, should be utilized to guarantee the uniqueness and interpretability of PPK parameter estimates.

INTRODUCTION

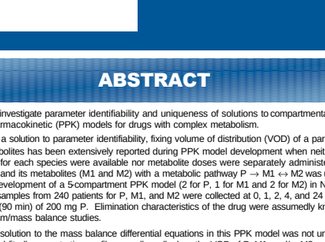
- Metabolite activity significantly contributes to the therapeutic and toxic effects of numerous medications.
- Use of population pharmacokinetic modeling to gain understanding of the behavior of agents with complex metabolism is hampered when data describing parent drug/ metabolite excretion patterns or disposition after metabolite administration are not available.
- When a compartmental pharmacokinetic approach is used to investigate population pharmacokinetics, mass balance equations are developed to describe the known metabolic pathways of the drug. Unique solutions to these equations are only feasible if sufficient information, including boundary conditions, is available. The term "parameter identifiability" has also been used to describe this problem.
- Various approaches have been described to handle this issue, including assignment of fixed ratios for parent drug clearance pathways, assumption of metabolite volumes of distribution, or lack of intact parent drug and/or metabolite excretion. These methods are often difficult to implement or lack physiologic relevance.
- The metabolic pathways for most drugs have usually been investigated when population pharmacokinetic analysis for both prodrug and active metabolites are to be performed. A new approach that utilizes this prior information to obtain unique solutions to mass balance differential equations is illustrated below based on a simulated Phase II dataset.

METHODS

Data

- Simulated Phase II clinical trial data
- 240 subjects administered 200 mg of hypothetical prodrug P via 90 minute IV infusion
- PK sampling performed at times 0, 1, 2, 4, and 24 hrs after the end of infusion **(Figure 1)**
- Assays performed to obtain P, M1, and M2 concentrations
- Excretion data not available
- Metabolite administration not performed

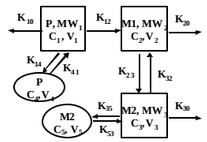
Figure 1: Simulated Observed Concentration-Time Profile of Drug P and Its Metabolites, M1 and M2



Model Structure

- Known metabolic pathways **(Figure 2)**
- Parent drug (P) as the reference for mass balance
- Molecular weight (MW) calibration on concentrations, all expressed as ng/mL as P

Figure 2: Model Structure Based on the Known Metabolic Pathways for Hypothetical Drug P



Mass Balance Differential Equations

$$\frac{dC_1}{dt}V_1 = Q_{inf} + K_4C_4V_4 - (K_{10} + K_{12} + K_{14})C_1V_1 \quad (1)$$

$$\frac{dC_2}{dt}V_2 = K_{12}C_1V_1 + K_{32}C_3V_3 - (K_{20} + K_{23})C_2V_2 \quad (2)$$

$$\frac{dC_3}{dt}V_3 = K_{23}C_2V_2 + K_{53}C_5V_5 - (K_{30} + K_{32} + K_{35})C_3V_3 \quad (3)$$

$$\frac{dC_4}{dt}V_4 = K_{14}C_1V_1 - K_4C_4V_4 \quad (4)$$

$$\frac{dC_5}{dt}V_5 = K_{35}C_3V_3 - K_{53}C_5V_5 \quad (5)$$

where C_i and V_i represent concentration and volume of distribution in the i^{th} compartment, respectively ($i = 1 \ldots 5$); K_{mn} represents the rate constant of the mass transport from the m^{th} compartment to the n^{th} compartment ($m, n = 1, \ldots, 5$); and Q_{inf} is the IV infusion rate, which can be expressed as: Q_{inf} = Dose/T when $t \leq T$ and 0 otherwise where T is the infusion duration (1.5 hours).

Pharmacostatistical Model

- First-order eliminations – conversion and excretion
- Re-parameterized in NONMEM® code: $CL_{mn} = K_{mn}V_m$
- Exponential random effects on CL_{10}, CL_{12}, CL_{20}, CL_{23}, CL_{30}, and CL_{32}
- Exponential error model for interindividual variability
- Proportional error model for residual variability
- NONMEM® v.5.1.1 was used for modeling and SAS® software, version 6.12, was used for statistics and graphs.

RESULTS

Non-unique Solutions

- Fitting of the model to the concentration data yielded infinite sets of solutions dependent on the initial estimates for various parameters.
  - These solutions simultaneously fit all 3 species equally well although the physiological relevance of the parameter estimates was different **(Figure 3)**.
- Pharmacokinetically, the problem of a non-unique solution results from insufficiency of data – no excretion data nor metabolite administration.
- Mathematically, the problem of a non-unique solution results from insufficiency of boundary conditions for the mass balance differential equations **(Equations 1-5)**.
- The problem cannot be effectively solved by fixing volumes of distribution because:
  - Parameter estimates are then physiologically meaningless (**Figure 4**);
  - Assumptions on volumes of distribution are not confirmable;
  - Volume of distribution is model-dependent; and
  - Solutions are still non-unique.
- However, this problem can be solved by fixing excretion ratios based on prior information or assumptions, which are confirmable, to:
  - constrain some PK parameters (see below) and
  - reduce the number of parameters to be estimated (**Equations 6 – 7**).

Figure 3: Model-Predicted Concentration-Time Profiles for P, M1, and M2 with Different Combinations of Volumes of Distribution

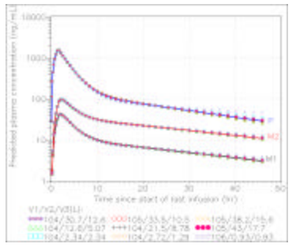
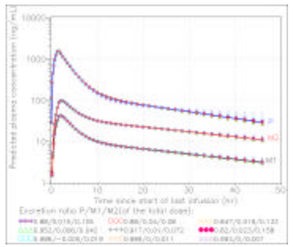


Figure 4: Model-Predicted Concentration-Time Profiles for P, M1, and M2 with PK Parameters at Different Excretion Ratios



Boundary Conditions

- Boundary conditions on excretion ratios (from prior information) set to: 84.7%, 1.91%, and 13.4% of the total dose (TD) excreted as intact P, intact M1, and intact M2, respectively.
- Constraints on pharmacokinetic parameters (**Equations 6-7**):

$$CL_{12} = (1.91\%+13.4\%)/84.7\%*CL_{10} = 0.18*CL_{10} \quad (6)$$

$$CL_{20} = 1.91\%/13.4\%*CL_{23}/(1+CL_{32}/CL_{30}) = 0.143*CL_{23}/(1+CL_{32}/CL_{30}) \quad (7)$$

Unique Solution with above Constraints:

- PK parameter estimates are unique, stable, and interpretable (**Table 1** and **Figure 5**).
- Accuracy of parameter estimates is linearly dependent on the accuracy of the assumed or previously measured excretion ratios (**Figure 6**).
- Relative position of individual PK parameters in the population distribution does not change with excretion ratios (**Figure 7**).
- Model-predicted excretion ratios are exactly as expected (**Figure 8**).

Table 1: Parameter Estimates and Standard Errors for the Pharmacokinetic Model

Parameters	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Estimate	%SEM	Estimate	%SEM
CL_{10} (L/hr)	20.9	6.8	30.2	17.7
CL_{12}/CL_{10}	0.180 Fixed	NA	NA	NA
CL_{12} (L/hr)	NA	NA	27.7	10.7
$CL_{20}/CL_{23}*(1+CL_{32}/CL_{30})$	0.143 Fixed	NA	NA	NA
CL_{23} (L/hr)	270	9.3	12.8	98.2
CL_{30} (L/hr)	19.0	9.7	NA	NA
CL_{32}/CL_{23}	0.254	4.5	NA	NA
CL_{32} (L/hr)	NA	NA	35.2	35.0
V_1 (L)	105	1.8	NE	NE
V_2 (L)	38.2	23.5	NE	NE
V_3 (L)	15.6	23.5	NE	NE
V_4 (L)	266	38.7	NE	NE
V_5 (L)	285	11.3	NE	NE
CL_{14} and CL_{41} (L/hr)	15.6	6.4	NE	NE
CL_{35} and CL_{53} (L/hr)	32.1	6.9	NE	NE
RV for P (%CV)	20.0	4.6	NA	NA
RV for M1 (%CV)	20.5	5.9	NA	NA
RV for M2 (%CV)	18.8	4.9	NA	NA

Note: NA = Not Applicable
NE = Not Estimable
RV = Residual Variability
%SEM = Percent Standard Error of the Mean = SE/Parameter Estimate*100%

Figure 5: Goodness-of-Fit for the Pharmacokinetic Model

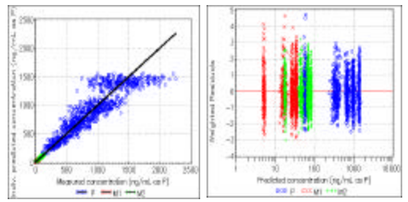


Figure 6: Relationship Between the Accuracy of Estimated Pharmacokinetic Parameters and Excretion Ratios Assumed or Measured in Prior Studies

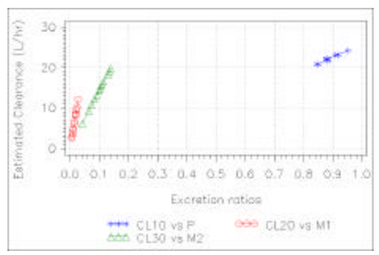


Figure 7: Lack of Effect of Excretion Ratios on the Relative Position of Individual PK Parameters in the Population Distribution (First 50 Patients)

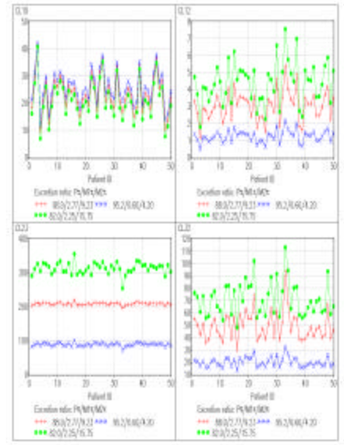
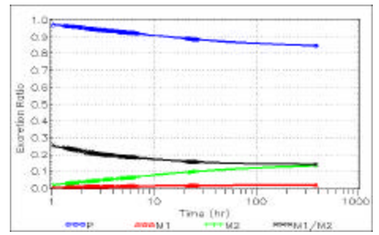


Figure 8: Model-Predicted Excretion Ratios versus Sampling Time Following Last Infusion



CONCLUSIONS

- Unique solutions to the mass balance differential equations describing compartmental pharmacokinetic models are not possible if sufficient information on excretion or metabolite administration is not available.
- Utilization of additional boundary conditions based on knowledge of excretion characteristics assumed or gained in prior mass balance or metabolic pathway studies is required to obtain unique solutions to the mass balance differential equations.
- Application of the approach described in this analysis could facilitate future clinical development of drugs with complex metabolism.

ACKNOWLEDGEMENT

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