W4232

Evaluation of Covariate Effects on Population Pharmacokinetics (PPK) of Both Parent Drug and Metabolite(s) from Clinical Trial Data without Metabolite Administration or Excretion Sampling

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ABSTRACT

Purpose. To evaluate the influence of covariates on the PPK of both parent drug and metabolite(s) from clinical trial data with neither separate metabolite administration nor excretion sampling.

Methods. A model drug (P) and its active/toxic metabolites (M1 and M2) with a metabolic pathway of P → M1 ↔ M2 plus intact excretion of all three species were used to simulate the evaluation of covariate effects on PK parameters of a 5-compartment model (2 for P, 1 for M1, and 2 for M2). A Phase II dataset was simulated, with 1690 P, M1, and M2 samples from 338 patients, collected around 0, 3, 7, 14, and 23 hr after an IV infusion (90 min) of 100 mg/m² P. The typical excretion characteristics of the drug were assumed or available from prior studies. Fifteen covariates on five clearances (parent and metabolites) were evaluated via NONMEM® V.

Results. The problem of parameter identifiability in simultaneous PPK modeling for both parent drug and metabolite(s) was best solved with assumptions or application of prior information on the drug excretion characteristics. Eight significant covariates were identified based on alpha=0.001, independent of the accuracy of the excretion ratios which linearly determined the accuracy of the PK parameter estimates. When different excretion ratios were assumed, the relative position of the individual PK parameter values in the population distribution of the PK parameter was unchanged. The relative significance of each covariate (defined as the ratio of the coefficient of the covariate to the typical PK parameter estimate) was not significantly changed with the excretion ratios.

Conclusions. The method of fixing excretion ratios as a solution to the problem of parameter identifiability does not significantly influence the identification of significant covariates for simultaneous estimation of PPK for parent drug and metabolite(s).

INTRODUCTION

- Metabolite activity significantly contributes to the therapeutic and toxic effects of numerous medications.
- Metabolite PK are important but difficult to quantify because urinary/fecal sampling or separate administration of metabolites are not performed in clinical trials.
- Simultaneous population pharmacokinetic modeling provides advantages over sequential modeling of metabolites to obtain insightful knowledge regarding metabolism and reversible biotransformation.
- An approach to obtain unique solutions to mass balance differential equations describing compartmental pharmacokinetic models using additional boundary conditions based on known or assumed excretion patterns has previously been described.[1-2]
- The influence of excretion characteristic assumptions about drugs with complex metabolism merits consideration when further applying this approach in covariate analysis.
- Accurate estimation of covariate effects on parent drug and metabolite PK facilitates understanding of interindividual variability and exposure-response relationships.

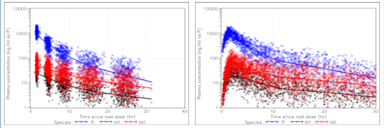
METHODS

Table 1: Simulated Phase II Clinical Trial Data

	Trial 1*	Trial 2
Number of subjects, 100 mg/m^2 90 min IV infusion	338	481
PK sampling at t hours (N(t,σ^2) or uniform) post-infusion	Uni(0,0.01), N(3,0.017), N(7,0.023), N(14,0.017), N(23,0.0064)	t=0.2-2, 2-5, 5-10, 10-18, 18-30 uniform distribution
Measured concentrations	P, M1 and M2	P, M1 and M2
Urinary/fecal sampling	No	No
Separate administration of metabolites	No	No
Distribution of continuous covariates	Normal	Normal

* Only results from Trial 1 are presented here.

Figure 1: Simulated Concentration–Time Profile of Drug P and Its Metabolites M1 and M2



Trial 1 Trial 2

- All concentrations calibrated with molecular weight and expressed in ng/mL as P

Figure 2: Model Structure

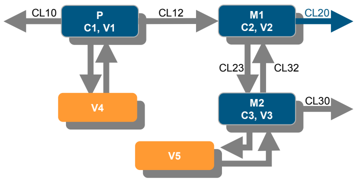


Table 2: Covariate Distributions

Covariates	mean±std error; median (min, max) or %(n)
Dose (mg)	191±27.7; 190 (131.4, 248.7)
Height (cm)	173±11.6; 172 (150.2, 199.7)
Weight (kg)	75.6±14.6; 75 (45.3, 125.3)
Age (years)	59.9±7.5; 60.2 (37.5, 80.2)
CLcr (mL/min)	94.8±24.3; 92.4 (40.3, 159.6)
BSA (m2)	1.91±0.28; 1.90 (1.31, 2.49)
AST (U/L)	26.2±9.2; 26.3 (5.4, 50.5)
Total Bilirubin (TBIL) (mg/dL)	0.61±0.18; 0.60 (0.2, 1.1)
Hemoglobin (HGB) (U/L)	14.3±2.2; 14.4 (8.2, 18.8)
Performance status (PS)	42.6%(144) PS0, 38.8%(131) PS1 and 18.6%(63) PS
Gender (SEX)	52.7% (178) male and 47.3% (160) female
Co-medication (COMED)	45.3% (153) no and 54.7% (185) yes
RACE	78.7% (266) Caucasian; 21.3% (72) other

Mass Balance Differential Equations

$$\frac{dC_1}{dt}V_1 = Q_{inf} + K_{41}C_4V_4 - (K_{10} + K_{12} + K_{14})C_1V_1$$

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

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

$$\frac{dC_4}{dt}V_4 = K_{14}C_1V_1 - K_{41}C_4V_4$$

$$\frac{dC_5}{dt}V_5 = K_{35}C_3V_3 - K_{53}C_5V_5$$

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

Pharmacostatistical Models and Covariate Evaluation Methods

- First-order elimination – metabolism and excretion
- Exponential error models for interindividual variability
- Proportional error models for residual variability
- Additive linear covariate effects (normalized and centered) evaluated on CL10, CL12, CL20, CL23, CL30, and CL32
- Either backward elimination (BE) from a full model or forward selection (FS) from a structural model followed by backward elimination (p=0.001)

Solutions to Parameter Identifiability Problem

- Prior information regarding excretion characteristics from mass balance studies:
  - P%:M1%:M2% and
  - P%+M1%+M2%=100%
- Constraints on PK parameters:
  - CL12/CL10=(M1%+M2%)/P%
  - CL20/CL30=M1%/M2%*AUC_{M2}/AUC_{M1}=M1%/M2%*CL23/(CL30+CL23)

NONMEM® Code Segment

- $PK

```
TVCL10 = THETA(1)          CL10 = TVCL10*EXP(ETA(1))
TVCL12 = 0.18*THETA(1)     CL12 = TVCL12*EXP(ETA(2))
TVCL20 = THETA(2)          CL20 = TVCL20*EXP(ETA(3))
TVCL23 = THETA(3)          CL23 = TVCL23*EXP(ETA(4))
TVCL30 = THETA(4)          CL30 = TVCL30*EXP(ETA(5))

TVCL32 = (0.40*TVCL23/TVCL20-1)*TVCL30
CL32 = TVCL32*EXP(ETA(6))
```

Table 3: Excretion Ratios Tested and Covariate Evaluation Methods Used

Cases	P%:M1%:M2%	(M1+M2)%/P%	M1%/M2%	Method
1	88.5%:1.50%:10.0%	0.13	0.15	BE
2	80.0%:6.67%:13.3%	0.25	0.50	BE
3	76.9%:3.85%:19.3%	0.30	0.20	BE
4	90.9%:3.41%:5.68%	0.10	0.60	BE
5	84.7%:4.36%:10.94%	0.18	0.40	FS+BE

RESULTS

Table 4: PK Parameter Estimates

case	1		2		3		4		5	
PK parameter	mean	std error	mean	std error	mean	std error	mean	std error	mean	std error
OFV	28903.281		28899.503		28899.703		28916.989		28898.912	
CL10	30.800	0.692	27.900	0.554	26.900	0.545	31.600	0.653	29.500	0.617
CL12/CL10	0.130	.	0.250	.	0.300	.	0.100	.	0.180	.
(CL30+CL32)/CL30*CL20/CL23	0.150	.	0.500	.	0.200	.	0.600	.	0.400	.
CL23	273.000	21.100	439.000	22.000	537.000	62.000	197.000	13.700	340.000	17.900
CL30	24.100	1.020	32.100	1.140	46.200	1.560	13.800	0.468	26.200	0.953
CL32/CL23	0.275	0.009	0.298	0.011	0.278	0.012	0.303	0.011	0.292	0.011
V1	112.000	1.810	111.000	1.660	111.000	1.710	111.000	2.020	111.000	1.710
V2	45.200	9.240	84.000	8.970	91.800	17.000	38.600	3.920	62.200	4.280
V3	8.930	6.760	12.300	5.520	17.100	12.600	5.410	3.210	10.400	2.570
V4	122.000	2.860	121.000	2.710	121.000	2.800	122.000	2.960	122.000	2.780
V5	234.000	10.700	387.000	15.200	463.000	18.300	174.000	6.790	297.000	12.400
CL14=CL41	15.600	0.418	15.600	0.414	15.600	0.417	15.600	0.401	15.600	0.403
CL35=CL53	34.600	2.160	57.000	2.560	68.500	3.470	25.700	1.120	44.100	1.530
Coeff of HGB on CL10	19.800	4.110	19.800	3.160	22.100	3.430	17.400	6.220	19.300	3.520
Coeff of PS2 on CL10	-7.740	1.430	-7.980	1.360	-8.570	1.710	-7.160	1.760	-7.790	1.400
Coeff of RACO on CL12	0.964	0.303	1.820	0.432	2.120	0.551	0.757	0.734	1.390	0.312
Coeff of HGB on CL32	90.700	22.800	156.000	32.800	181.000	46.700	70.700	13.700	120.000	20.800
Coeff of CRCL on CL10	7.520	2.300	7.520	2.490	7.510	2.860	7.620	2.300	7.640	2.120
Coeff of COMED on CL23	-53.000	27.200	-91.600	21.200	-105.000	69.200	-41.700	15.600	-68.100	16.000
Coeff of COMED on CL30	4.350	2.310	5.250	2.310	8.110	4.690	2.250	0.688	4.460	2.080
Coeff of HGB on CL12	-1.660	0.657	-2.070	1.030	-3.040	1.270	-1.260	2.540	-2.450	0.751
Coeff of TBIL on CL12	.	.	.	.	.	.	.	.	1.110	0.518
Coeff of PS1 on CL10	-3.130	1.430	-3.040	1.410	-3.030	1.760	-3.090	1.340	-3.070	1.070
Coeff of PS2 on CL32	-23.000	7.540	-38.200	10.900	-46.100	16.600	-16.700	16.600	-29.100	7.860
Coeff of PS2 on CL12	0.724	0.217	1.040	0.262	1.400	0.407	0.439	0.673	0.808	0.350
Coeff of AST on CL10	-2.960	2.310	-3.000	1.600	-3.110	2.120	-2.920	1.970	-3.020	1.080
Coeff of TBIL on CL30	-11.400	8.280	-18.700	4.460	-22.600	9.160	-8.460	1.600	-9.820	2.170
Coeff of SEX on CL12	0.322	0.306	0.591	0.357	0.734	0.469	0.000	.	.	.
ETA1 on CL10	0.126	0.011	0.157	0.013	0.171	0.015	0.119	0.010	0.138	0.012
ETA2 on CL12	0.100	0.012	0.100	0.011	0.096	0.010	0.109	0.014	0.105	0.011
ETA3 on CL20	0.000	.	0.000	.	0.000	.	0.000	.		
ETA4 on CL23	0.136	0.030	0.116	0.030	0.129	0.031	0.113	0.035	0.118	0.028
ETA5 on CL30	0.173	0.025	0.248	0.031	0.180	0.023	0.279	0.037	0.223	0.028
ETA6 on CL32	0.127	0.058	0.159	0.053	0.139	0.057	0.166	0.068	0.157	0.052
EPS1 on P	0.047	0.003	0.048	0.002	0.048	0.002	0.047	0.002	0.048	0.002
EPS2 on M1	0.055	0.004	0.052	0.003	0.054	0.003	0.052	0.003	0.053	0.003
EPS3 on M2	0.041	0.003	0.041	0.003	0.041	0.003	0.042	0.003	0.041	0.003

Figure 3: Goodness-of-Fit Graphs

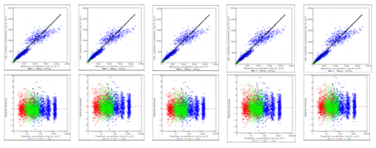


Figure 4: PK Parameter Distributions (First 50 Subjects)

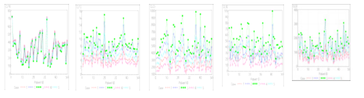


Figure 5: Relative Magnitude of Covariate Effects versus Typical Values of PK Parameters

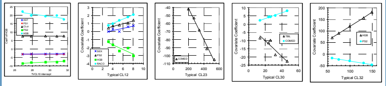
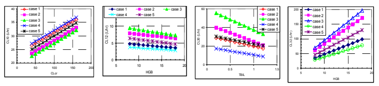


Figure 6: Effect of Excretion Ratios on Covariate Effects



In Trial 2, regardless of excretion characteristics utilized, all significant covariates were identified (BE).

CONCLUSIONS

- Covariates which should have been identified as significant were identified in all cases, except one marginally significant covariate.
- Relative magnitude of covariate effects are similar in all cases.
- The above conclusions are independent of the PK sampling schedule.
- The above conclusions are independent of covariate evaluation methods: BE vs FS+BE.

REFERENCES

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