Simultaneous Population Pharmacokinetic Modelling of Parent Compound and Metabolite in Plasma and Urine for a New Drug Candidate

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Introduction

In the first human studies of a new drug candidate, extensive blood and urine sampling was performed in order to characterise the pharmacokinetics of the parent compound and its' major metabolite in healthy subjects. It was observed that the plasma concentrations of the major metabolite in some instances peaked earlier than the parent compound.

Objectives

To construct a model that could describe the population pharmacokinetics of a new drug candidate and its major metabolite. Since the major metabolite apparently peaked earlier than the parent compound for many of the subjects, special attention was on the absorption of the parent compound and the metabolite.

Dataset

Data from 4 different phase I studies were included in the population pharmacokinetic analysis. Study designs consisted of both single dose (2 studies) and multiple dose studies (2 studies). The doses given ranged from 10 to 75 mg for single dosing and 2.5 to 60 mg for multiple dosing. Total number of subjects was 113. Demography of the subjects are given in Table 1.

Table 1. Demography of the 113 healthy subjects

	Mean (SD)	Median	Range
Age (yr)	28.8 (12.6)	25	18-77
BMI (kg/m^2)	24.0 (2.6)	24.1	19.2-29.4
CL_{CR} (mL/min)	125 (35)	121	60-219
Height (cm)	176 (10)	176	150-198
Lean body mass (kg)	57.3 (9.5)	58.7	35.8-78.4
Weight (kg)	74.6 (11.9)	75	47-105
	Counts (frequency)		
Males	77 (68 %)		
Females	36 (32%)		
Asian	4 (4 %)		
Black	6 (5 %)		
Caucassian/Hispanic	101 (89%)		
Other	2 (2 %)		

Blood and urine sampling

Extensive bloodsampling was peformed for all subjects, with on average 36 samples/subject (range 7-106), up to144 hours after last dosing. Urine was collected in 67 of the113 subjects. The urine was either collected after single dosing or after mulitple dosing or both, up to 48 hours after last dosing. Plasma and urine content of parent compound and metabolite was determined with a validated HPLC method.

Modelling

It was neceassary to include gastrointestinal metabolism In order to allow the metabolite to peak earlier than the parent compound. Part of the parent compound was assumed to be metabolised to the major metabolite in the gastrointestinal tract (k_{gmet}), whereby both the parent compound and the metabolite were absorbed (k_a and k_{amet}, respectively). The structural model consisted of a central compartment for both parent compound and metabolite (V3 and V5, respectively), peripheral compartments (V4 and V6) and urine compartments The structural model is schematically illustrated in Figure 1. All processes were modelled as first-order.

Interindividual variability (IIV) was modelled as exponential terms on k_a, k_{amet}, V3, CL, CL_R, V4, CL_{met} and CL_{Rmet}. A combined proportional and additive residual error model was used for the metabolite data, while a proportional residual error model was used for the parent compound data.

Modelling continued

NONMEM VI (Globomax) was used for the modelling (ADVAN 6.TRANS=1). Due to very long run times with First Order Conditional Error minimization method (FOCE), several days, the first order (FO) minimization method was used. File managing, running and post-processing of NONMEM was done with an in-house developed system, based on Perl and S-PLUS®.

Figure 1. Structural model for parent compound and metabolite combined

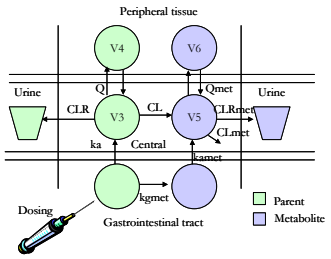
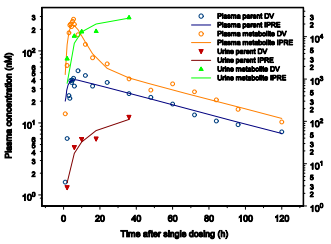


Figure 2. Indivually observed and predicted data for one subject after single dosing.



Results

The model adequately described the data, although there was a tendency that the urine data was overpredicted (see Figure 3). Q_{met} and V6 was fixed to values from other more simplified models, in order to get the model to converge. Overall, large IIV was seen, while the residual variability was moderate to low.

Table 3. Parameter values with relative standard errors

Parameter	Final Parameter		Interindividual Variability (%CV)	
	Mean	%RSE	Final estimate	%RSE
k_a (h^{-1})	0.21	13	67	19
k_{gmet} (h^{-1})	0.048	10	ne	ne
k_{amet} (h^{-1})	0.47	15	135	41
V3 (L)	780	7.8	126	21
CL (L/h)	30	6.8	42	15
CL_R (L/h)	0.13	18	36	31
Q (L/h)	200	6.9	ne	ne
V4 (L)	1800	7.7	34	36
Q_{met} (L/h)	6.0	Fixed	ne	ne
V5 (L)	46	15	ne	ne
CL_{met} (L/h)	36	23	89	31
CL_{Rmet} (L/h)	21	40	81	57
V6 (L)	10000	Fixed	ne	ne
RV^1	14	12	na	na
RV^2	2.7	26	na	na
RV^3	20	12	na	na

RSE relatiel standard error
ne not estimated
na not applicable
[1] residual variability metabolite proportional (%)
[2] residual variability metabolite additive (nM)
[3] residual variability parent proportional (%)

Conclusion

A model was created that adequately describe the population pharmacokinetics of the parent compound and the major metabolite for a new drug candidate. The model indicates that the parent compound undergoes gastrointestinal metabolism, which can explain the observation that the major metabolite in many cases apparently peaks before the parent compound.

Figure 3. Goodness-of-fits plots for the population pharmacokinetic model

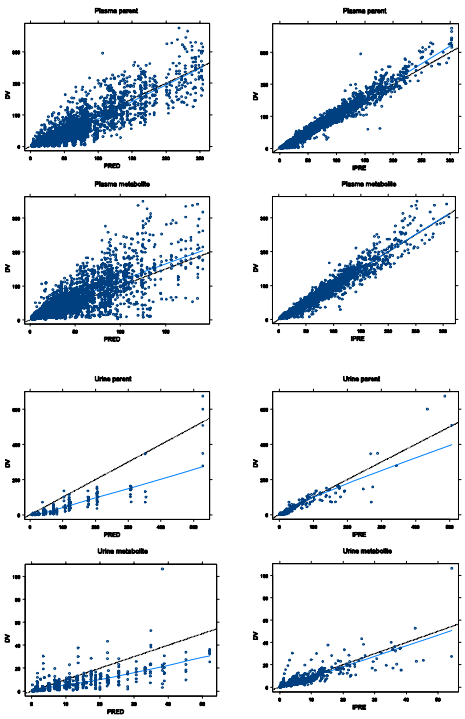


Table 3. Relevant outtrack of the NONMEM control file

```
$SUBROUTINE ADVAN6 TRANS=1 TOL=4

$MODEL NCOMP=8
COMP=(DEPOT)    COMP=(DEPOT)
COMP=(CENTRAL) COMP=(PERIPHER)
COMP=(CENTRAL) COMP=(PERIPHER)
COMP=(URINE)    COMP=(URINE)

$PK
KA=THETA(1)*EXP(ETA(1))
KGMET=THETA(2)
KAMET=THETA(3)*EXP(ETA(2))
V3=THETA(4)*EXP(ETA(3))
CL=THETA(5)*EXP(ETA(4))
CLR=THETA(6)*EXP(ETA(5))
Q=THETA(7)
V4=THETA(8)*EXP(ETA(6))
QMET=THETA(9)
V5=THETA(10)
CLMET=THETA(11)*EXP(ETA(7))
CLRMET=THETA(12)*EXP(ETA(8))
V6=THETA(13)
S3=V3 S5=V5 S8=1000

$DES
DADT(1)=-KA*A(1)-KGMET*A(1)
DADT(2)=KGMET*A(1)-KAMET*A(2)
DADT(3)=KA*A(1)-Q/V3*A(3)+Q/V4*A(4)-CL/V3*A(3)-CLR/V3*A(3)
DADT(4)=Q/V3*A(3)-Q/V4*A(4)
DADT(5)=CL/V3*A(3)+KAMET*A(2)-QMET/V5*A(5)+
    QMET/V6*A(6)-CLMET/V5*A(5)-CLRMET/V5*A(5)
DADT(6)=QMET/V5*A(5)-QMET/V6*A(6)
DADT(7)=CLR/V3*A(3)
DADT(8)=CLRMET/V5*A(5)

$ERROR
IPRE=F
IF(CMT.EQ.8.OR.CMT.EQ.5) THEN
Y=IPRE*(1+ERR(1))+ERR(2)
ELSE
Y=IPRE*(1+ERR(3))
ENDIF
```

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