Population pharmacokinetic model development and evaluation after nevirapine administration to mothers and newborns

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Background and Objectives

Within a prevention of mother-to-child transmission (PMTCT) programme in Uganda[1] an antiretroviral prophylaxis with nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor, was administered to HIV-positive pregnant women at labour and their newborns. NVP concentrations were determined in three different matrices: plasma of mother and newborns and breast milk. The aim of the population pharmacokinetic (PK) analysis was to develop PK models for mothers and for newborns that adequately described the data. Based on selected key PK models different diagnostic tools were used to assess model performance.

Subjects and Methods

Study characteristics

62 HIV-positive pregnant women and newborns participated in the PMTCT programme (Tab.1). Total NVP concentrations in milk and plasma were determined by a validated LC-tandem MS method.[2] Sampling schedule comprised time points at delivery, week 1 and 2 for the three matrices (Fig.1).

Population pharmacokinetic data analysis and evaluation

For PK model development 113 plasma and 95 breast milk samples of mothers and 113 plasma samples of newborns were available. Population PK analyses for mother and newborns data were separately performed using the NLME modelling approach implemented in NONMEM™ V/VI, (ADVAN6 Trans1 TOL5; FOCE with interaction). Xpose, version4_4.0-6.1, R2.8.1 and MS-Excel were used to evaluate model performance using the diagnostic tools: goodness of fit (GOF) plots and visual predictive checks (VPC).

Tab. 1: Characteristics of the study and its population (ID = subject) including number or median, range and number of missing data.

Characteristic	Statistical values		Missings
Number of IDs	total	124	
	male/female	36/88	0
Age* [years]	median	26	4
	min. – max.	16 - 39	
Weight mother [kg]	median	56	0
	min. - max.	42 - 84	
Birth weight newborn [kg]	median	3.1	1
	min. - max.	2.0 – 3.9	
Breast feeding	yes/no	54/8	0
NVP_{mother} to birth [h]	median	5.1	0
	min - max	0.3 – 24.8	
Birth to $NVP_{newborn}$ [h]	median	0.9	0
	min - max	0.1 – 40.6	
NVP_{mother} to $NVP_{newborn}$ [h]	median	8.5	0
	min - max	1.3 – 46.0	

* only mothers

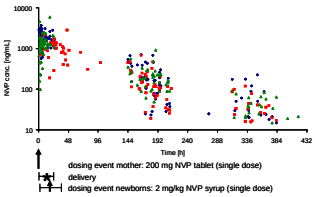

Fig. 1: Sampling times for mother plasma (blue), breast milk (red) and plasma of newborns (green). Arrows depict dosing events and asterisk the delivery of newborns.

Results

In the model building process various structural models were investigated (Fig. 2, 5, 8). As key model (I) a 2-compartment (CMT) model was developed for maternal (mo) data to combine plasma (central CMT, V2) and milk (peripheral CMT, V3) data. Since the NVP transfer from V2 to V3 was very rapid, unidirectional transfer between V2 and V3 was explored revealing no improvement. Hence, data of the two matrices were lumped into one CMT (key model II). For newborns (ch) a 1-CMT model had already been developed (III).[3] First-order input and elimination processes were found to be the most appropriate (I-III). Due to sparse data, the absorption rate constant K12 was fixed to 1.66/h (I-III).[4] All estimated parameter values are shown in Tab. 2 with RSEs ≤49% for mo and ch.

I. mo: bidirectional transfer with rate constants (K23, K32) between V2 and V3 were implemented plus an additional clearance term (K30) which was switched on after delivery.

II. mo: 1-CMT model combining NVP plasma and breast milk concentrations in the central CMT V2.

III. ch: two different NVP input routes with one for the plasma/placenta transfer using a 'bioavailability' factor (F') and a second for the oral dose of the newborns.

The results of the evaluation are presented for the different matrices in Fig. 3+4, 6+7 and 9+10 (I-III).

Tab. 2: Population pharmacokinetic estimates of NVP obtained from the final models (left/middle: mother plasma and milk, right: newborn plasma).

Model parameter	Units	Population estimates: mother (I)	RSE[a], %	Population estimates: mother (II)	RSE[a], %	Population estimates: child (III)	RSE[a], %
FIXED EFFECTS							
K12	[h^{-1}]	1.66 fixed	-	1.66 fixed	-	1.66 fixed	-
F'	%	-	-	-	-	17.8	17.8
V2/F	[L]	12.2	7.2	110.0	4.5	25.8	20.0
V3/F	[L]	-	-	-	-	-	-
K23	[h^{-1}]	9.2	8.0	-	-	-	-
K32	[h^{-1}]	1.14	15.1	-	-	5.1	47.8
K20	[h^{-1}]	0.09	11.9	0.014	4.6	-	-
K30	[h^{-1}]	0.004[b]	41.0	-	-	-	-
CL1/F	[$L \cdot h^{-1}$]	-	-	-	-	0.3	18.0
RANDOM EFFECTS							
Interindividual Variability							
ω K20	[% CV]	31.9	25.1	28.8	21.3	-	-
ω K30	[% CV]	38.2[b]	48.8	-	-	-	-
ω V2/F	[% CV]	16.4	43.1	22.0	41.7	28.6	25.8
ω F'	[% CV]	-	-	-	-	58.5	29.1
Residual Variability							
σ proportional	[% CV]	35.4	7.0	35.4	7.0	40.9	17.9
σ additive	[ng/mL]	1.0 fixed	-	0.001 fixed	-	2.0 fixed	-

[a] Relative standard error (standard error divided by population estimate ·100; for the random effects parameters RSE is related to the corresponding variance scale)
[b] Parameter estimation only for breast feeders and time > delivery

I. Population PK analysis of maternal data: bidirectional 2-CMT model

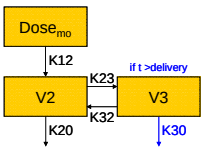

Fig. 2: Schematic structural model for maternal data including bidirectional transfer.

The appropriateness of the bidirectional model is depicted in the GOF plot in Fig. 3. Overall, data points spread around the line of identity with a tendency of underestimation for small concentrations. The VPC also revealed this tendency for plasma and breast milk (Fig. 4), but suggests adequate model performance.

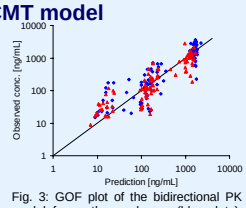

Fig. 3: GOF plot of the bidirectional PK model for mothers: plasma (blue dots), breast milk (red dots).

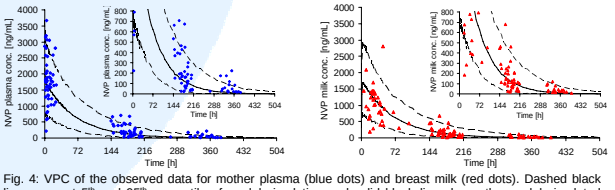

Fig. 4: VPC of the observed data for mother plasma (blue dots) and breast milk (red dots). Dashed black lines present 5th and 95th percentile of model simulation and solid black line shows the model simulated median. Insets: y-axis present smaller concentrations.

II. Population PK analysis of maternal data: 1-CMT model

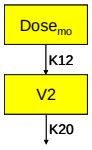

Fig. 5: Schematic structural 1-CMT model for maternal data.

GOF plot of the 1-CMT model (Fig. 6) showed similar results as key model (I) with the tendency of understimation of concentrations at later time points (week 2). The 90% prediction interval of the VPC for both matrices was smaller than in key model (I), while no bias in the central tendency was observed (Fig. 7) comparable to key model (I).

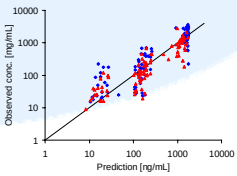

Fig. 6: GOF plot of the 1-CMT PK models for mothers: plasma (blue), milk (red).

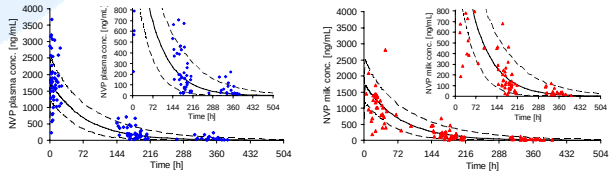

Fig. 7: VPC of the observed data for mother plasma (blue dots) and breast milk (red dots). Dashed black lines present 5th and 95th percentile of model simulation and solid black line shows the model simulated median. Insets: Insets: y-axis present smaller concentrations.

III. Population PK analysis of newborn data: 1-CMT model

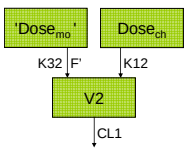

Fig. 8: Schematic structural model for newborn data including two different input routes of NVP.

The appropriateness of the model for newborn data is presented by GOF plot (Fig. 9). The VPC for newborn plasma data overall demonstrated no bias of the central tendency and a minor overprediction of variability of model parameters (Fig. 10).

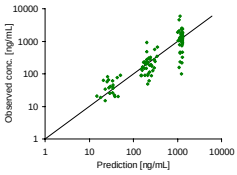

Fig. 9: GOF plot of the final PK models for newborn plasma data (green dots).

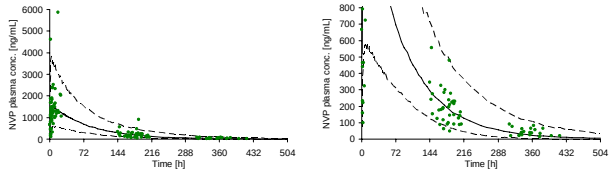

Fig. 10: VPC of the observed data for newborn plasma (green dots). Dashed black lines present 5th and 95th percentile of model simulation and solid black line shows the model simulated median. Right panel: y-axis present smaller concentrations.

References [1] Karcher H. et al. MedGenMed, 8: 12 (2006) [2] Stocker H. et al. AntiAgChem., 48: 4148 (2004) [3] Frank M. et al. PAGE 17, Abstr 1249 (2008) [4]Kappelhoff BS. et al. Antivir.Ther., 10: 145 (2005).

Conclusion

Different population PK models for mother plasma/breast milk were developed. Ultimately, the most parsimonious 1-CMT model showed no disadvantage compared to more complex PK models. Due to the sparse data situation -until now- it was not possible to obtain adequate population estimates representing the physiological situation of the changes during birth and lactation. The model evaluation suggests sufficient model performance for maternal and newborn data. Based on final PK models simulations will be performed to assess dosing regimes for newborns to guide prevention strategies of HIV transmission from mother-to-child.

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