Nevirapine - Population pharmacokinetic model building and simulation for mothers and newborns

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Background and Objectives

A clinical trial was performed in Uganda to assess the risk of intra-partum and postnatal transmission of HIV by antiretroviral prophylaxis. Nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor, was given as single oral dose.

Since breastfeeding is popular in sub-Saharan Africa in addition to plasma, breast milk concentrations might be of particular importance. Therefore, NVP was 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 the final PK models simulation scenarios were performed to assess the entire concentration-time profiles and the maintenance period of NVP concentrations in different individuals.

Subjects and Methods

Study characteristics

62 HIV-positive pregnant women and their newborns participated in a prevention of mother-to-child transmission (PMTCT) of HIV programme in Uganda (Tab.1)[1].

Women received a 200 mg NVP tablet within 48 h before delivery and newborns received 2 mg/kg of NVP syrup within 3 d after birth. Total NVP concentrations in milk and plasma were determined by a validated LC-tandem MS method[2]. Sampling schedule comprised timepoints at delivery, week 1 and week 2 for the three matrices. (Fig. 1).

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

		Study population	Missings
number of IDs	total	124	0
	male/female	36/88	
age* (years)	median	26	4
	min. – max.	16-39	
weight* (kg)	median	56	0
	min.-max.	42-84	
race	black	124	0

* only mothers

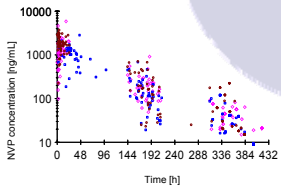

Fig. 1: Sample times for mother plasma (brown, breast milk (blue) and plasma of newborns (pink).

Pharmacokinetic data analysis

For PK model development 113 plasma and 95 breast milk samples of mothers and 113 plasma samples of newborns were available. Population PK analysis for mother and newborns data were separately performed using the NLME modelling approach implemented in NONMEM™ V, level 1.1 (ADVAN6 Trans1 TOL5; FOCE with interaction). Xpose, version4_4.0-6.1 and MS-Excel were used to assess the goodness of fit (GOF).

Simulation

Final PK models were used for simulating entire concentration-time profiles. Different percentiles ($P_{0.05-0.95}$) of the individual PK parameter distributions were used for simulation in NONMEM™.

Results

Population pharmacokinetic analysis of maternal data

The PK model building process for concentration-time courses started with the generation of a structural PK model (Fig.2, left). An integrated 2 compartment PK model was developed for the combined mother plasma and breast milk data. First-order input and elimination processes were found to be the most appropriate for the data. Due to sparse data, the absorption rate constant K12 was fixed to 1.66/h[3].

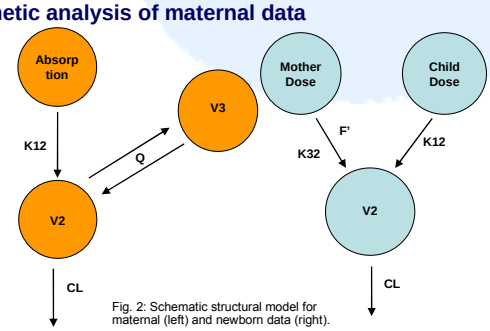

Fig. 2: Schematic structural model for maternal (left) and newborn data (right).

The total distribution volume (V/F:104.3 L) included the central (plasma mother, V2/F: 9.0 L) and peripheral (breast milk, V3/F: 95.3 L) compartment linking drug transfer by an inter-compartmental clearance (Q/F) being very high: 122 L/h. An inter-individual variability (IIV) was implemented in clearance of NVP (CL/F: 1.45 L/h with 29% CV for IIV) that was estimated using an exponential random-effects model. Residual variability was modelled using a combined error model.

Population pharmacokinetic analysis of newborn data

A first simplified structural 1-compartment model (Fig. 2, right) fitted the plasma data of newborns best. The maternal input routes (NVP tablet to mothers via either the blood/placenta-barrier or via breast milk) were combined using a 'bioavailability' (F': 18% with 58.5% CV for IIV, being implemented by restricting individual values ≤ 100%. Additionally, on V2/F (plasma of newborn, 25.8 L) an IIV of 28.6% CV was implemented and resulted in a first adequate final model.

The low elimination capacities for NVP and together with the distribution volumes resulted in long half-lives of 50.3 h for mothers and 60.6 h for newborns, respectively.

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

Model parameter	Units	Population estimate, mother	RSE[a], %	Population estimate, newborn	RSE[a], %
FIXED EFFECTS					
K12	[h^{-1}]	1.66 fixed	-	1.66 fixed	-
F'	%	-	-	17.8	17.8
V2/F	[L]	9.0	26.7	25.8	20.0
V3/F	[L]	95.3	5.1	-	-
Q/F	[$L \cdot h^{-1}$]	122	18.9	-	-
K32	[h^{-1}]	-	-	5.1	47.8
CL/F	[$L \cdot h^{-1}$]	1.45	5.1	0.3	18.0
RANDOM EFFECTS					
Interindividual Variability					
ω CL/F	[% CV]	29.0	19.2	-	-
ω V2/F	[% CV]	-	-	28.6	25.8
ω F'	[% CV]	-	-	58.5	29.1
Residual Variability					
σ proportional	[% CV]	37.8	6.0	40.9	17.9
σ additive	[ng/mL]	0.01 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)

All estimates and their relative standard errors (RSE) are shown in Tab. 2. For maternal data, RSEs of the fixed- and random-effects parameter were generally very small (5-27%) indicating a high precision; for newborn data the RSE of K32 (transfer rate constant for NVP plasma/placenta and plasma/milk) and of IIV for CL/F revealed higher values.

The appropriateness of the final models was also demonstrated by GOF plots (Fig. 3). In all regions maternal (left panel) and newborn data points (right panel) were spread around the line of unity. Generally, all plots indicate that the models adequately described the datasets.

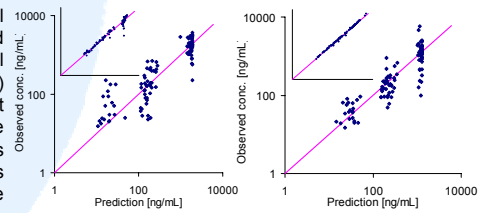

Fig. 3: GOF plots of the final PK models for mother plasma/breast milk (left panel) and for newborn plasma (right panel). Insets: x-axis show individual predictions.

Simulation

Entire concentration-time profiles for individuals with different PK properties (i.e. $P_{0.05,\ CL/F,ind}$ - $P_{0.95,\ CL/F,ind}$ for mothers and $P_{0.05,\ V2/F,ind}$ - $P_{0.95,\ V2/F,ind}$ for newborns) were simulated. For newborns 2 additional scenarios were evaluated: (i) "minimum concentration" with $P_{0.95,\ V2/F,ind}$ plus $P_{0.05,\ F'\ ind}$ and (ii) "maximum concentration" with $P_{0.05,\ V2/F,ind}$ plus $P_{0.95,\ F',ind}$. Simulations revealed long-term NVP exposure >IC_{90} (16 ng/mL) for 10-24 d (mothers) and 12-22 d (newborns), respectively (Fig. 4).

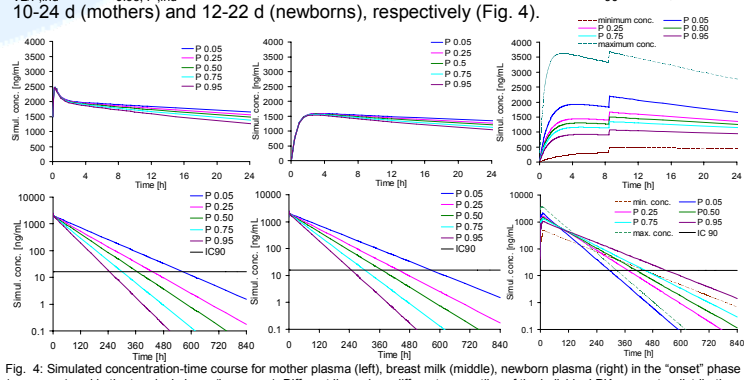

Fig. 4: Simulated concentration-time course for mother plasma (left), breast milk (middle), newborn plasma (right) in the "onset" phase (upper row) and in the terminal phase (lower row). Different lines show different percentiles of the individual PK parameter distribution for CL/F (mothers) or V2/F (newborns); left plots of lower/upper row also include combinations of percentiles of F' and V2/F representing 'minimum concentrations' and 'maximum concentrations' scenarios: see text.

References

[1] Karcher H. et al. MedGenMed, 8: 12 (2006) [2] Stocker H. et al. AntiAgChem., 48: 4148 (2004) [3] Kappelhoff BS et al. Antivir.Ther., 10: 145 (2005).

Conclusion

A population PK model for mother plasma/breast milk was successfully developed and a first model proposed for newborn plasma data. To comprehensively describe the different input routes in newborns further modelling investigations have to be carried out. Based on the 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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