Mega-model of nevirapine population pharmacokinetics

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Background

❖ A **mega-model** utilizes multiple sources of raw data. Without the need for new clinical studies, mega-models can address novel research questions and add power for covariate detection. A challenge is accounting for variability and factors caused by the differences between the data sources.

❖ **Nevirapine** (NVP) is currently the most commonly used antiretroviral drug[1]. Despite the availability of adequate PK data, important questions, including drug-drug interactions and genetic polymorphisms, still require further investigation.

Objective

To develop a mega-model of NVP PK in a population of HIV-infected South African adults on anti-retroviral therapy (ART) and investigate modelling strategies to jointly analyse data from different sources.

Methods

Data: PK-data from three different sources (Table 1) were analyzed. The patients were recruited from public ART-programs in Western Cape, South Africa, on an ART-regimen including 200 mg NVP BID and sampled at steady state. The data included rich and sparse sampling schedules, day and night samples, fed and fasted doses, presence and absence of concomitant rifampicin-based antitubercular therapy. All samples were analyzed by the same laboratory. In total 115 individuals and 1107 samples were included.

Table 1. Summary of patients characteristics (median and range when applicable).

	Study 1[2]	Study 2[3]	Study 3[4]
Type of study	Interaction with tuberculosis (TB) treatment including rifampicin	Therapeutic drug monitoring of directly observed therapy	Interaction with malaria drugs artemether /lumefantrine
Subjects	49	50	16
Age [years]	34 (21-58)	32 (19-75)	32 (28-60)
Male/Female	12/37	4/46	3/13
Weight [kg]	67 (43-102)	72 (47-128)	60 (45-80)
Sampling [hours after first observed morning dose] (dosing 12 hourly)	*Rich (n=25):* predose, 0.5, 1, 1.5, 2, 4, 6, 10,12, 12.25, 12.75, 14, 22, 24 *Sparse (n=24):* 2 samples 0-12, median: ~3	1 sample 0-12, median: ~2	predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 14, 24, 60, 61.5, 62, 63, 64, 65, 66, 68, 70, 72, 96, 120, 144
Visits for sampling	1 during TB-treatment, 1 after TB-treatment, 1 for control group of patients without TB	1-4 per subject, 6 months apart	1

Modeling: A non-linear mixed effects model was implemented in NONMEM 7. A stepwise development approach was used:

- ❖ exploratory analysis to identify study-specify features
- ❖ combining rich data (from Study 1 and 3)
- ❖ stepwise addition of sparse data (Study 1 and 3, then Study 2)

Each dose was regarded as a separate occasion. Model development was guided by goodness of fit metrics and VPCs.

Missing data: Since height was not recorded for some subjects (study2), a regression model describing the relationship between gender, body weight (BW) and fat free mass (FFM, height required for calculations[5]) was developed and used to impute FFM.

Results

Table 2. Final parameter estimates (variability as CV, precision as RSE%) and bootstrap results (n=200, stratified on study, precision as RSE%).

	Parameter estimates (RSE%)		Bootstrap (RSE%)	
CL/F pop. 1 [L/h•(kg FFM/42 kg)^0.75]	3.12	(5.1)	3.16	(6.0)
CL/F pop. 2 [L/h•(kg FFM/42 kg)^0.75]	1.45	(14.7)	1.45	(15.8)
Probability [%] to belong to pop. 2	17.3	(45.3)	19.3	(48.1)
V/F [L•(kg BW/70 kg)]	105	(4.9)	105	(5.4)
MTT [h] fed	2.46	(7.5)	2.46	(7.1)
MTT [h] fasted	0.596	(8.7)	0.599	(9.0)
F [%] when on TB-treatment	61.3	(8.7)	61.7	(8.7)
Prop error [%]	8.41	(5.4)	8.39	(4.8)
BSV CL/F [%]	24.9	(13.9)	23.9	(16.0)
BSV F when on TB-treatment [%]	34.1	(27.0)	31.2	(33.2)
BOV F [%]	26.9	(9.6)	26.5	(10.7)
BOV MTT [%]	64.0	(9.1)	63.3	(9.1)

❖ **Absorption** described with transit compartment model[6] (the number of transit compartments fixed to two).

❖ **Fasted doses** absorption about four times faster compared to fed doses.

❖ **Allometric scaling** of clearance with FFM (exponent=0.75) and of volume of distribution with body weight (exponent=1).

❖ **Mixture model** with two populations to describe differences in clearance. This is possibly due to the effect of genetic polymorphisms (for example 516G>T in CYP2B6[7]) on NVP clearance.

❖ **Effect of TB-treatment** decreased bioavailability by about 40% with a BSV of 34% CV. An effect on clearance was evaluated and found not to describe the data as well.

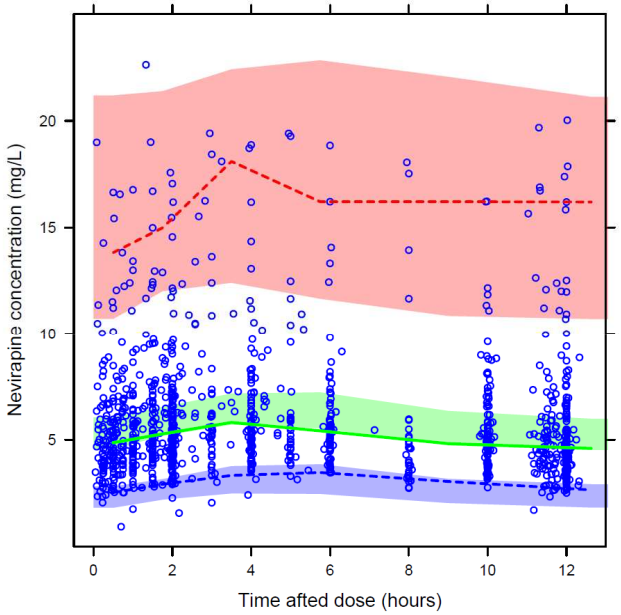

Figure 1. Prediction and variability corrected VPC. The prediction used for the correction is the weighted average of the prediction in the two sub-populations.

Conclusions

❖ A model of oral NVP PK data from three different sources was developed and resulted in low residual variability and good precision in parameter estimates, indicating the feasibility of mega-models.

❖ Further data from diverse sources (including different ethnicities) are needed to create a true mega-model.

❖ A mixture model could be used to describe large differences in clearance between patients. This effect can probably be explained by genetic polymorphisms and a mixture model is an option when genotyping data is unavailable. Our estimated probability (17.3%) of belonging to the low clearance population agreed well with the earlier reported prevalence of T/T homozygotes for the CYP2B6 516G>T polymorphism in the South African population[8].

❖ Concomitant rifampicin-based antitubercular therapy and fed/fasted dosing conditions significantly impact NVP PK.

References: [1] WHO, *Toward universal access, scaling up priority HIV/AIDS interventions in the health sector*, 2009 [2] Cohen *et al.* J Antimicrob Chemother, 61, 2008 [3] Nachenga *et al.* AIDS, 24, 2010[4] Kredo *et al.* 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 2010, abstract N-140 [5] Andersson & Holford, Annu Rev Pharmacol Toxicol, 48, 2008 [6] Yu *et al.*, Int J Pharm, 140, 1996 [7] Rotger *et al.* Pharmacogenet Genomics, 15, 2005 [8] Cohen *et al.* Antivir Ther, 14, 2009