

In silico estimation of oral bioavailability: Implications to estimation of efavirenz PK parameters.

Tafireyi Nemauro*



*Department of Clinical Pharmacology, College of Health Sciences, University of Zimbabwe.



Background:

The time space has been used as the basis of the rate-defining variable in model formulation.

Covariates have been taken as additives and their inclusion into the structural model has been investigated stepwise through backward/forward elimination regression methods.

It is noted that the covariate space is possibly the most significant space in the modeling and estimation of PK parameters.

A covariate measure is developed based on frequencies using PLS regression (SIMCA). That is, a highly correlated variable is formulated from a series of covariates linked to the response variable.

- Consequently, this variable is used for identification of PK/PD response spaces.
- An important parameter that is oral bioavailability (f) based on a fixed cumulative uptake-volume (V) associated with full absorption is estimated *in silico*.

This is noted to considerably affect the resultant parameter estimates and accuracy of the population dependent variable estimates.

Objectives:

To develop methods/models that give rise to better parameter estimates

Materials and Methods:

Gender, weight and *CYP2B6*, *516G>T* genetic data, plasma middose concentration (x) of 61 patients on 600mg dose of efavirenz containing HAART was collated and analysed.

Multivariate data analysis and correlations between variables were done to determine the relative contributions of gender, weight and *CYP2B6* genetic polymorphism.

Models were derived to guide dose adjustment in patients predicted to have unsafe drug exposure.

Furthermore models were derived to estimate PK parameters that include bioavailability, elimination rate constant, volume of distribution and AUC (A one compartment model is used) using NONMEM, Partial Least Squares Regression, and Regression methods.

Results:

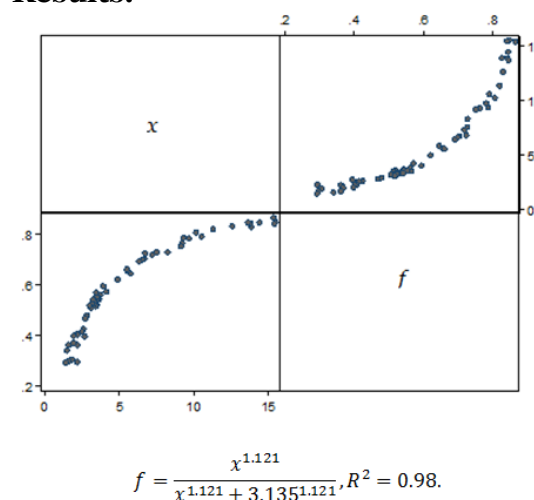


Figure 1. Estimated bioavailability and middose plasma conc. (at steady state) Basic goodness-of-fit plots

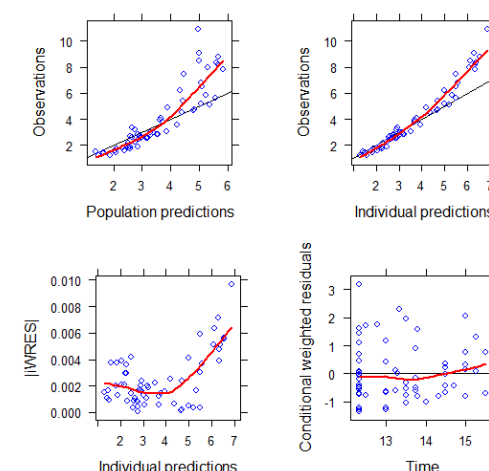


Figure 2. Goodness of fit plot of plasma conc corrected for accumulation

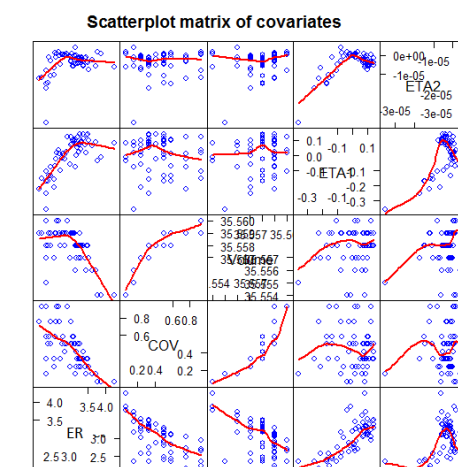


Figure 3. Scatter plot ER-elimination rate at the point of full absorption, COV-covariate measure from PLS

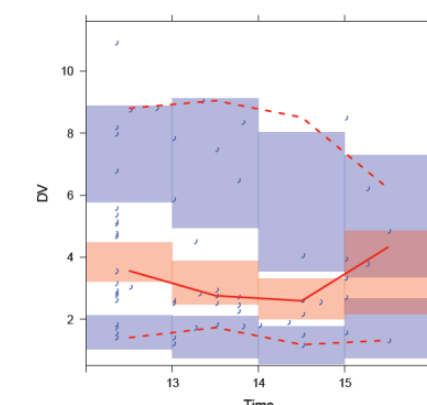


Figure 4. VPC plot

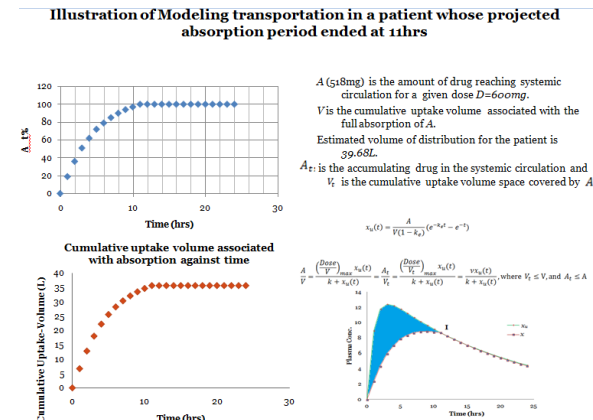


Figure 5. Projected transportation, absorption and estimated pharmacokinetic curve in a patient with bioavailability of 0.86.

Table 1.

The estimated and projected AUC and AUCs for efavirenz categorised according to the most significant variable *CYP2B6* *G516T* investigated in the separation of observed plasma concentrations in this population sample for the 61 patients.

GENOTYPE	Efavirenz plasma conc. $\mu\text{g/ml}$ median(IQR)	AUC mg.h/L median(IQR)	AUC ₀₋₂₄ mg.h/L median(IQR)
GG	3.32(1.62,3.64)	84.16(57.83,101.50)	96.77(65.21,120.23)
<i>CYP2B6</i> <i>G516T</i> GT	3.49(2.81,6.14)	89.55(77.51,127.11)	115.42(97.53,178.52)
TT	8.70(5.01,11.40)	150.56(98.91,180.88)	240.69(149.00,297.11)

The following correlations were noted of the observed middose plasma concentration at steady state, bioavailability and elimination rate constant, $\rho(x, f)=0.92$, $\rho(x, k_e)=-0.88$, and $\rho(f, k_e)=-0.83$.

Conclusions:

Estimation of oral bioavailability improves predictions of efavirenz plasma concentrations. Efavirenz is a drug that is well distributed in the fluid volume system. These conditions are modeled through the covariate measure.

References:

- Nyakutira, C., *et.al*. High prevalence of the *CYP2B6* 516G-->T(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *European journal of clinical pharmacology*, (2008). 64(4), 357-65.
- Nemauro, T., *et. al*. Impact of gender, weight and *CYP2B6* genotype on efavirenz exposure in patients on HIV/AIDS and TB treatment: Implications for individualising therapy. *African Journal of Pharmacy and Pharmacology*, (2012). 6 (29), 2188-93.
- Kriegel, J. M., *et.al*. Multivariate modeling of cytochrome P450 3A4 inhibition. *European journal of pharmaceutical sciences*, (2005). 24(5), 451-463
- Haenlein, M., *et. al*. A Beginner's Guide to Partial Least Squares Analysis. *Understanding Statistics*, (2004). 3(4). 283-297

Acknowledgements:

Pharsight Student Sponsorship, College of Health Sciences (University of Zimbabwe), Novartis sponsored Pharmacometrics workshops in Africa, AIBST, C. Nhachi, C. Masimirembwa and G. Kadzirange.

