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

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**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)

**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.**

<table>
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<th>Gender, weight and CYP2B6, 516G&gt;T genetic data, plasma middose concentration (x) of 61 patients on 600mg dose of efavirenz containing HAART</th>
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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:**


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