Development of a population pharmacokinetic model for Atazanavir in drug using subjects

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Abstract

- **Purpose:** Atazanavir (ATV) is one of the antiretroviral drugs most frequently used in the treatment of AIDS. This study aimed to develop a structural pharmacokinetic population model for atazanavir. Additional analysis focused on the development of a covariate model (characteristics which 'explain' PK variability) for an HIV-infected drug user patient population.
- **Method:** A structural model was developed using NONMEM on the full profiles of 20 non-HIV infected subjects who were given a single oral dose of ATV/ritonavir (200 samples). The model discrimination was based on the objective function value (OFV), goodness of fit, and parameter estimates. A covariate model was developed using the forward inclusion backward elimination method ($p<0.025$) on a second dataset with 66 HIV-infected subjects (315 samples) who used ATV as part of their anti-HIV therapy.
- **Result:** A two-compartment model with first order absorption, Lag-time, inter-subject variability and heteroscedastic residual error, was found to be a better fit ($R^2 = 0.974$ with IPRED) than a one-compartment model with the same properties (-62.4 OFV). Using the HIV-infected population, an effect of ritonavir on the clearance and an inter-occasion variability were added to the model before testing the other covariates. Our final model includes an effect of ritonavir and aspartate aminotransferase (AST) on the atazanavir clearance ($p<0.01$). No other covariate effects were significant.
- **Conclusion:** Most ATV PK models in the literature have only used a one-compartment pharmacokinetic models. Our study showed that the predictions of ATV concentration could be improved by the use of a two-compartment model including the effect of AST and RTV as covariates on the clearance.

Introduction

- Atazanavir (ATV) is a protease inhibitor used in the treatment of HIV disease[1].
- Abuse of injectable drugs is a significant HIV infection and transmission risk factor. These drugs may affect the PK of prescribed drugs and the adherence of drug abuse patients to medical treatment is often poor[2].

Objective

- Our study aimed to develop a structural PK population model for ATV. Additional analysis were then conducted to develop a covariate model in an HIV-infected drug user population.

Datasets

Two datasets were obtained from TDM and drug interaction study sponsored by the National institute on Drug Abuse (NIDA):

- One dataset contained 200 measures of ATV plasma concentrations from 20 non HIV-infected drug users subjects following a single oral dose.
- The second dataset contained 323 measures of ATV plasma concentrations for 68 HIV-infected drug users subjects. The samples were collected on 3 different occasions for each subject in multiple oral dose with co administration of anti HIV drugs.

PK Meta Analysis

- A PK meta analysis was performed to get prior information on:
  - The linearity of AUC with dose,
  - Structure of the PK models used,
  - Initial estimates of the models parameters,
  - The significant covariates.

PK Modeling Strategy

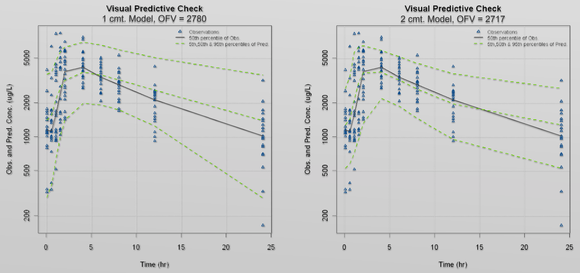
- The datasets were formatted using R v2.14.2.
- A structural population PK model was developed using NONMEM v7.1.0 and the information of the meta analysis, on the rich dataset.
- The model selection was based on parameters value, goodness of fit and objective function value decrease.
- The structural model predictions were assessed using Visual Predictive Check (VPC).
- The Beal Methods 1 and 3 were tested for the data below quantification limit.
- The base model was then be applied to the HIV-infected subjects population and a covariate selection was performed using the forward selection (α=5.0%) , backward deletion method (α=1.0%).

The Base Model

- Using the prior information different parametric and statistical models were evaluated on our small dataset with rich sampling.
- A one and a two compartment model with first order absorption and elimination and lag time with inter subject variability and heteroscedastic residual error were the two candidates selected.

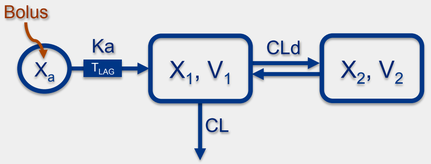
	Population parameter estimates						Inter subject % Coefficient of Variation					
Model	CL/F (L/h)	V1/F (L)	V2/F (L)	Q/F (L/h)	Ka (1/h)	ALAG1 (h)	CL	V1	Q	KA	ALAG1	Res Err %
1 cmt.	5.24	88.2	-	-	1.49	0.890	28.5	21.5	-	68.1	55.9	17.6
2 cmt.	5.72	56.8	304	7.06	0.790	0.820	29.8	15.7	56.5	108	61.2	13.3

- For each of those two models, VPC were constructed with the 90% CI of the predictions after a 1000 subject simulation, using the final population model.



The Base Model (cont'd)

- The two compartment model (below) was found give a better description of the data and have been selected to be the base model.



- Some additions were made to this base model before the covariate selection:
  - An effect of RTV on CL was added (inhibits clearance),
  - An inter occasion variability (IOV) was implemented on CL and V1.

The HIV-Infected Subjects Dataset

- The base model was run on the new dataset and the following observations were made:
  - Some errors were found in the dosing history and corrected, a non compliance from those subjects was assumed,
  - Two subjects were found to be outliers and were excluded from the dataset.
- The M1 method was found to be more robust and selected for our model.

The Covariates Selection Process

- The following covariates were assessed on CL and V1
  - **Demographic:** Gender, Age, Ethnicity, Weight and Body Mass Index.
  - **Genetic:** X3A5.GT, GT.3435 and GT2677 (CYP450 mutations).
  - **Pathophysiologic:** AST, ALT, Bilirubin and Albumin concentrations, Hepatitis B and/or C co-infection.
  - **Environmental:** NRTI, NNRTI, smoking, alcohol, cocaine, methadone and marijuana.
- The covariates effect were explored graphically and then evaluated one by one on the base model using the forward selection method.
- Due to the important number of significant covariates at α=5% we decided to be more restrictive and use an α=2.5% to build the full model.

The covariates shown in this table are significant at α=5%, the ones in blue are significant at α=2.5%.

Model	OFV change/base model
AST on CL	-12.778
Albumin concentration on CL	-7.245
ALT on CL	-7.016
Methadone use on CL	-5.593
Hepatitis B and C+ on CL	-5.437
Bilirubin levels on CL	-4.742
Gender on CL	-4.470
Smoking on CL	-4.405
NNRTI on CL	-3.915
Caucasian on CL	-3.850

The Backward Deletion

- The full model was built by adding the effects of AST, ALT, albumin, methadone and co-infection with hepatitis B and C on the clearance.
- The backward deletion step was performed at the risk α=1.0%.

The Backward Deletion (cont'd)

Model	OFV change	Results
Removed effect of **Hepatitis B and C+** on CL	+ 1.94	N.S.
Removed effect of **Methadone** use on CL	+ 3.47	N.S.
Removed effect of **ALT** on CL	+ 0.03	N.S.
Removed effect of **Albumin** concentration on CL	+ 2.50	N.S.

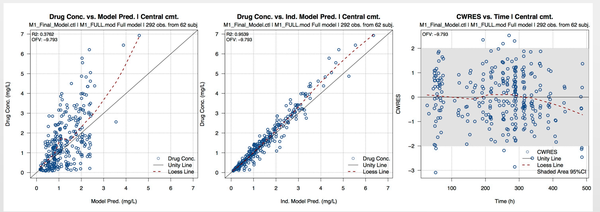
- The only significant covariate was found to be the Aspartate transaminase levels on the clearance.

The Final Model

The final parameter estimates of the final model are shown bellow:

Population parameter estimates								Inter subject % Coefficient of Variation					Inter Occasion Var. (%)		
CL/F (L/h)	V1/F (L)	V2/F (L)	Q/F (L/h)	Ka (1/h)	ALAG 1 (h)	RTV Effect On CL	AST Effect On CL	CL	V1	Q	KA	ALAG 1	CL	V1	Res Err %
28.8	28.5	706	8.64	0.150	0.800	-19.7	0.0700	34.2	139	55.4	31.9	19.2	34.4	168	27.2

Goodness of fit plot were also used to evaluate the predictions:



Conclusion

- According to our observation, a 2 compartment model allows a significantly better fit of our data than a 1 compartment.
- RTV and AST effect on CL were found to be the only significant covariates.
- Model misspecification were observed especially at high concentrations.
- A question remains: could it be due to a non linearity PK or the subjects' compliance?

References

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2 - E.F. McCance-Katz et al. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug and Alcohol Dependence 91, 269-279 (2007).

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