Population pharmacokinetic model for Ritonavir in HIV-infected patients treated with Lopinavir/Ritonavir (Kaletra®)

PAGE 2009

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INTRODUCTION

Kaletra® is a fixed dose coformulation of two HIV-1 protease inhibitors (lopinavir [LPV] 400mg/ritonavir [RTV] 100mg). The pharmacoenhancing effect of RTV on LPV resulted in a highly potent, clinically effective antiretroviral drug with a high genetic barrier to viral resistance.

OBJECTIVE

Having the population model previously obtained for LPV with the same data-set (D Santos Buelga. PAGE 2009), the aim of this study was to develop and validate a population pharmacokinetic (PK) model for RTV used as a booster in HIV-infected patients treated with Kaletra®

METHODS

PATIENTS: HIV-infected subjects, treated with Kaletra® twice daily

ANALITICAL ASSAY: HPLC with UV detection.

PHARMACOKINETIC ANALYSIS:

✓ **PK Model**: one-compartment model with first-order absorption and elimination including the absorption lag-time (ALAG)

✓ **PK parameters estimated**: Clearance(CL/F),distribution volume (V/F), Ka, ALAG

✓**Error model**: Proportional (interindividual) and additive (residual)

✓ **Software**: NONMEM V.I (FOCE, Interaction); Xpose (GAM)

✓**Covariates analysed**: age, sex, height, total body weight (TBW), body mass index (BMI), LPV trough concentration (CL_{LPV}), LPV clearance (CL_{LPV}), total bilirrubin, hepatitis C virus co-infection (HCV), and concomitant saquinavir (SQV), tenofovir (TFV) and atazanvir (ATV)

EXTERNAL VALIDATION: Comparison of model-predicted and observed concentrations obtained in the validation data. Mean prediction error (MPE) and standardised mean prediction errors (SMPE) were used.

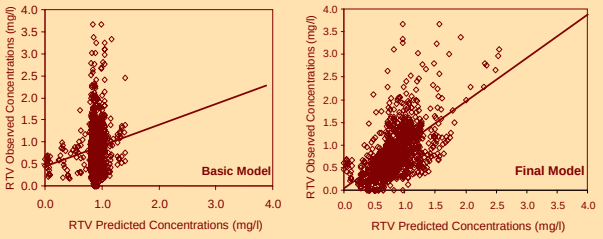
	INDEX SET	VALIDATION SET
N° patients (male/female)	198 (110/88)	65 (37/28)
N° RTV and LPV concentrations - Trough steady-state - From full PK profiles N° SQV/TFV/ATV concentrations	954 539 415 288/80/136	156 108 48 48/60/22
HCV (Y/N)	455/499	91/65
Age (years)	40.0 ± 8.18	42.2 ± 9.30
Weight (kg)	69.2 ± 14.6	68.6 ± 12.4
BMI (kg/m²)	23.9 ± 4.21	23.4 ± 3.40
LPV concentration (mg/l) RTV concentration (mg/l)	7.92 ± 3.45 0.86 ± 0.57	7.36± 3.61 0.79± 0.53
LPV clearance (CL_{LPV}) (l/h)	4.30 ± 1.4	5.33 ± 1.58

Demographic and clinical data of patients included in this study

RESULTS

BASIC and FINAL MODELS

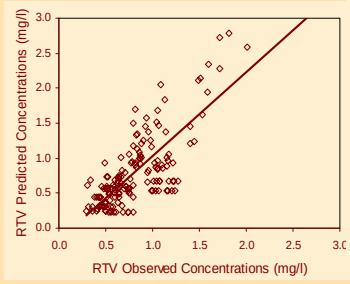
Parameter	Basic model (OF=-658.656) Mean (SE)	Final model (OF=-820.039) Mean (SE)
Structural model		$CL/F=\theta1*CL_{LPV}+\theta2^{SQV(0/1)}$ $V/F=\theta3$
ALAG (h)	2.49 (8.7)	2.44 (5.0)
Ka (h^{-1})	2.19 (45.7)	2.06 (14.7)
CL/F (l/h)	8.91 (3.7)	-
CL, $\theta1_{CL_{LPV}}$	-	2.15 (2.5)
CL, $\theta2_{SQV}$	-	1.25 (7.5)
V/F, θ3 (l)	330 (16.4)	303 (12.0)
Variance model		
Residual (SD)	0.13 (6.2)	0.12 (5.7)
Intersubject Ka (CV%)	65.9 (154.9)	65.1 (61.8)
Intersubject CL/F(CV%)	45.1 (13.9)	30.1 (14.2)
Intersubject V/F (CV%)	101.5 (21.5)	86.0 (19.1)



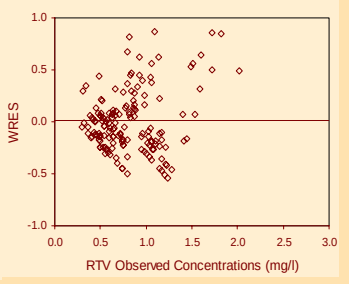
RTV Observed vs Predicted concentrations with the basic and final models

VALIDATION

MPE ± SD = - 0.013 ± 0.347 mg/l
SMPE ± SD = - 0.001 ± 0.299



Predicted vs Observed concentrations of RTV



WRES vs Observed concentrations of RTV

CONCLUSIONS

- Inclusion of the absorption lag-time leads to the best fitting for the basic model.
- The inclusion of CL_{LPV} in the model elicited a decrease in the objective function value (-658.66 to -801.18) and a reduction in the interindividual variability of RTV clearance (45% to 29%)
- RTV clearance was also significantly influenced by SQV concomitant treatment as a categorical covariate (0/1). This effect has been quantified (RTV clearance decreased by 25%).
- No covariates were found to explain the high variability of other PK parameters estimated.
- The validation results obtained confirm the adequacy of the proposed model.

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