Journal of the International AIDS Society

Poster presentation

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Modelling the change in lopinavir apparent oral clearance over time following cessation of lopinavir/ritonavir: data from the TAIL study

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from Ninth International Congress on Drug Therapy in HIV Infection
Glasgow, UK. 9–13 November 2008

Published: 10 November 2008

Journal of the International AIDS Society 2008, **11**(Suppl 1):P241 doi:10.1186/1758-2652-11-S1-P241

This abstract is available from: http://www.jiasociety.org/content/11/S1/P241

Purpose of the study

The TAIL study determined plasma concentrations of lopinavir/ritonavir (LPV/RTV) over 72 hours following cessation of LPV/RTV (400/100 mg twice daily) in healthy volunteers. There was a rapid decline in LPV concentrations as RTV diminished over time [1]. Here we have determined a model to quantify the changes in LPV apparent oral clearance (CL/F) in relation to RTV concentrations.

Methods

Plasma LPV and RTV concentrations were determined by HPLC-MS/MS. Initially, non-linear mixed effects modelling was applied (NONMEM vs. VI) to LPV and RTV data separately using first-order conditional estimation with interaction. Secondly, individual predicted RTV pharmacokinetic (PK) parameters were fed into a model to determine LPV PK parameters assuming competitive inhibition by RTV. Model fit was assessed by statistical and graphical methods. A decrease in minimal objective function value (OFV) of 3.84 points corresponded to a statistically significant difference between hierarchical models.

Summary of results

Sixteen healthy volunteers (six female) were included. A one-compartment model with zero-order absorption was used to generate RTV parameters. Initially, a one-compartment first-order absorption model was used for LPV in the combined model; however, under-prediction of concentrations in the early absorption phase and over-prediction in parts of the elimination phase occurred. A one-compartment zero-order absorption model for LPV improved the fit (OFV -157.934) and was parameterised by LPV clearance in the absence of inhibitor (CL0), apparent volume of distribution (V/F), CL/F and RTV inhibition constant (Ki) with inter-individual variability (IIV) included on CL0 and V/F. Residual error was described by a combined additive-proportional model. A first-pass model produced similar estimations. Parameter estimates and time-dependent changes in LPV CL/F are shown (Table 1; Figure 1, respectively). Larger changes in LPV CL/F were observed from approximately 10 hours post-dose com-

Table 1: Parameter estimates and standard errors.

Parameter	Estimate	Standard Error
CL0 (L/h)	53.2	8.09
Ki (mg/L)	0.0442	0.0102
V/F (L)	124	8.90
IIV CL0 (%)	16.2	9.69
IIV V/F	12.8	8.67
Residual error – proportional (%)	28.8	12.6
Residual error – additive (mg/L)	0.0117	0.00849

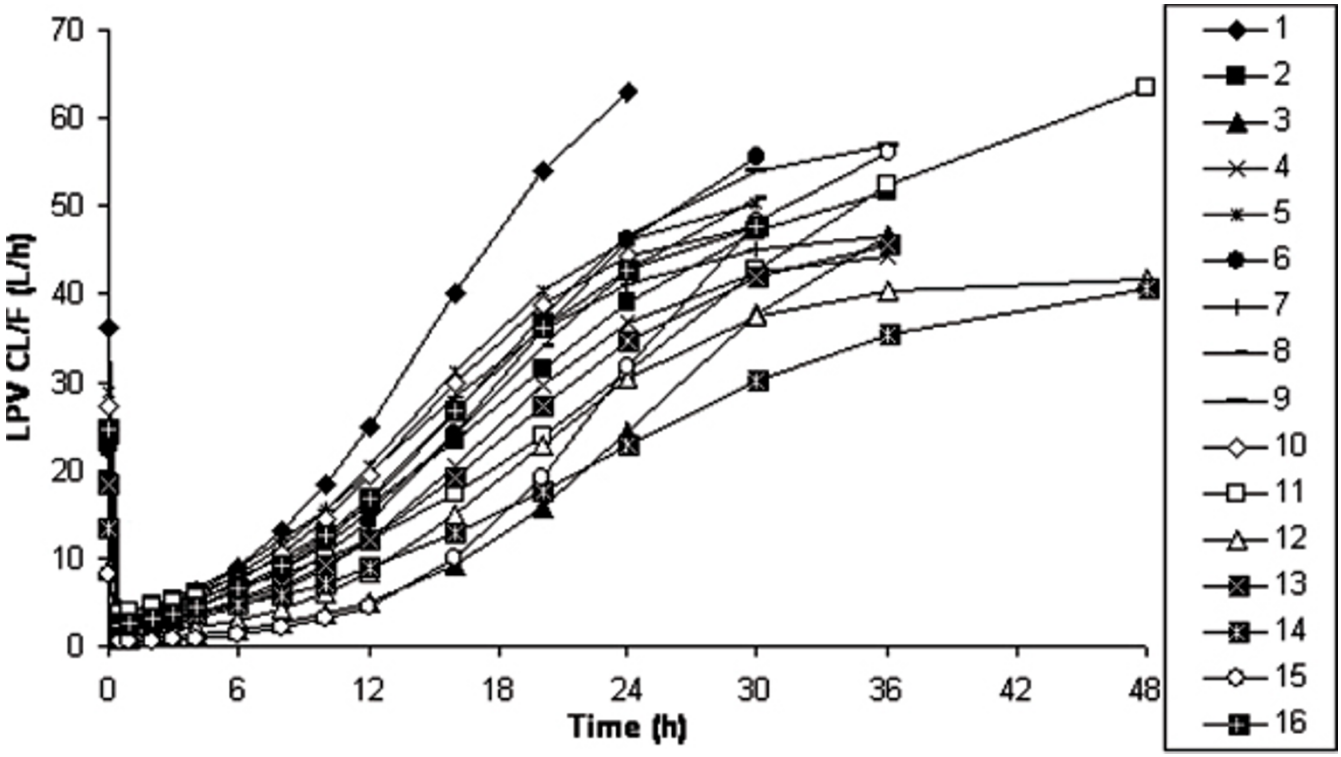

Figure 1
Time-dependent changes in LPV CL/F following drug cessation.

pared to 0.5–8 hours post-dose (3.04–63.83 vs. 0.40–12.99 L/h).

Conclusion

A model assuming competitive inhibition of LPV by RTV combined with zero-order kinetics best described the time-dependent changes in LPV CL/F following drug cessation. Given the complexity of the LPV-RTV interaction, potentially more complex models should be explored.

References

1. Boffito M, *et al.*: *AIDS* 2008 in press.