Simplifying Therapeutic Drug Monitoring for Twice Daily Regimens of Kaletra™

C. Alexander, J. Montaner, J. Asselin, L. Ting, K. McNabb, M. Harris, S. Guillemi, P. Harrigan.

B.C. Centre for Excellence in HIV/AIDS, University of British Columbia, Vancouver, Canada

ABSTRACT

E-mail address of presenting author: calexa@hivnetubc.ca

Background: Cost and inconvenience limit the application of full pharmacokinetic (PK) analysis in therapeutic drug monitoring. In this retrospective study, we explore whether lopinavir (LPV) exposures can be adequately estimated based on limited sampling.

Methods: 118 PK profiles from 92 patients on salvage therapy including twice daily LPV/RTV were analyzed. Two or more analyses were included from 22 patients where a regimen change was expected to alter exposure. After a minimum of 2 weeks on a stable regimen, blood was drawn immediately before, and at 1, 2, 4, 6, 8, 10 and 12 hours after a timed, observed medication dose. Plasma drug concentrations were determined by a validated HPLC-MS-MS assay. PK parameters (AUC^{0-12}, C_{12h}) were entered into linear regression models to determine the best correlation with LPV and RTV concentration at a single time point and the best correlation using a maximum of 2 time points (forward selection model). Adjusted jackknife standard deviations (sd) for the fitted AUCs were determined.

Results: Patients were taking a median 5 (IQR: 46) antiretrovirals including at least one other PI or NNRTI. Importantly, 91 (77%) of the PK profiles were obtained when patients were concurrently taking an NNRTI and/oramprenavir. The mean steady state (± CV) trough (C12h) and AUC(0 -12) were 4246 ng/mL (± 72%) and 73,600 h·ng/m L (± 47 %) respectively for LPV and 201 ng/m L (± 109 %) and 5,200 h·ng/mL (± 64 %) for RTV. In linear regression analyses, the AUC^{0-12} was best correlated with a single plasma LPV concentration at 8 hrs (r^2= 0.90, sd = 11,000). For 2 time points, the correlation was maximized when 2 and 8 hr data were included (r^2 = 0.97, sd = 5,300). A single 10 hr plasma concentration provided the best correlation with C12h (r^2= 0.91, sd = 919) with no significant improvement with additional data.

Conclusion: LPV exposures can be accurately estimated (± 5,300 h·ng/mL) from 2 plasma samples collected 2 and 8 hours after dosing for patients on twice daily LPV/RTV .

BACKGROUND

- Currently LPV/RTV is monitored in B.C. by generating full 12 h PK profiles.
- Blood is collected just prior to the morning dose and then again in 1, 2, 4, 6, 8, 10 and 12h after the morning dose.
- In the interests of cost and convenience, we investigated differentapproaches to estimating AUC using reduced blood collection strategies

Methods

- Patients selected for this retrospective study (N = 92) were all taking Kaletra twice daily as part of their regimen and underwent a full 12 hour pharmacokinetic assessment at the PK clinic between 02/01 and 10/02.
- Plasma LPV concentrations were determined by a validated, simultaneous assay using reverse phase high pressure liquid chromatography coupled with tandem mass spectroscopy (HPLC-MS-MS).
- PK profiles were generated and AUCs were determined using the linear trapezoidal rule and C_{min} was derived from the concentration measured at 12 hours after the observed morning dose.
- Linear regression models were used to determine the best correlation of AUC with the following: 1) concentrations at a single time point, 2) concentrations at a maximum of two time points, 3) the minimum number of chronologically determined concentrations necessary to achieve an $R^2 > 0.9$
- Adjusted jackknife standard deviations (Adj JK STD) for the fitted AUCs were determined.

Results

- 118 PK profiles from 92 patients were used in the analyses. Repeat patient assessments were used when a change in drug regimen was expectedto result in a change in drug exposure (e.g. Changed dose, co-administered NVP, EFV, DLV etc).
- The majority of study patients were undergoing multi drug rescue therapy (85%) with the median five antiretrovirals per regimen (IQR:4 -6, range 3-8).
- For the majority of patients, Kaletra was administered as recommended with LPV/RTV dosing ratios of 400/100 b.i.d of 533/133 b.i.d.

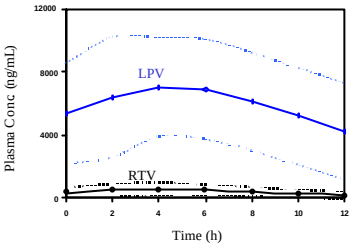
Table 1: Cohort Characteristics at the time of TDM assessment

% Male	**92**
Median Age (IQR)	**43.3 (39.6 – 48.5)**
Median Weight (Kg) (IQR)	**72.5 (68 – 84.3)**
Median Height (cm) (IQR)	**175 (171 – 182)**
Median Log(Viral RNA) (IQR)	**2.08 (1.70 – 3.40)**
Median CD4 count (cells/mL) (IQR)	**275 (150 – 380)**
Median Years Antiretroviral Experience (IQR)	**6.1 (5.1 – 8.6)**

Table 2: Concurrent PIs and NNRTIs

Drug	No. of Pk Profiles
None	**19**
NVP	**31**
DLV	**21**
EFV	**15**
IDV	**8**
APV	**6**
APV + NVP/EFV	**8**
Other	**10**

Figure 1: Mean Pharmacokinetic Profiles (with standard deviations) for LPV and RTV



LPV: CORRELATION WITH AUC

Table 3: Linear Relationships (AUC = $\Sigma m_i C_i + b$)

Time Point C_i	Coefficient m_i	Intercept b	R^2
C_0	9.64	21,389	0.778
C_1	9.57	19,429	0.785
C_2	8.50	18,867	0.6931
C_4	9.80	3,491	0.822
C_6	10.40	1,644	0.887
C_8	10.69	8,002	0.904
C_{10}	10.60	19,569	0.859
C_{12}	10.14	31,321	0.780
C_2, C_8	3.61, 8.11	734	0.97
C_0, C_1, C_2, C_4	4.83, 0.25, 0.04, 6.87	- 4,036	0.95

Figure 2: Calculated vs. Observed AUCs using C_8

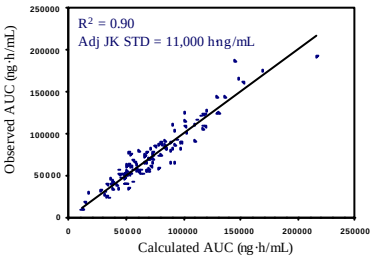


Figure 3: Calculated vs. Observed AUCs using C_2 and C_8

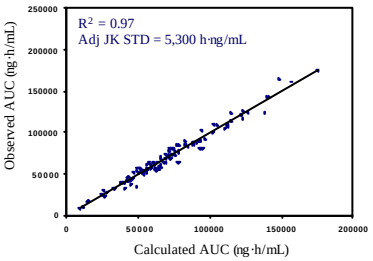
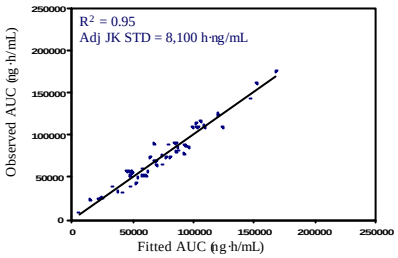


Figure 4: Calculated vs. Observed AUCs using C_0, C_1, C_2 and C_4



RTV: CORRELATION WITH AUC

Table 4: Linear Relationships (AUC = $\Sigma m_i C_i + b$)

Time Point C_i	Coefficient m_i	Intercept b	R^2
C_6	8.35	799	0.80
C_2, C_8	3.80, 7.26	394	0.90
C_0, C_1, C_2, C_4	4.00, 1.07, 0.92, 4.59	108	0.95

Figure 5: Calculated vs. Observed AUCs using C_2 and C_8

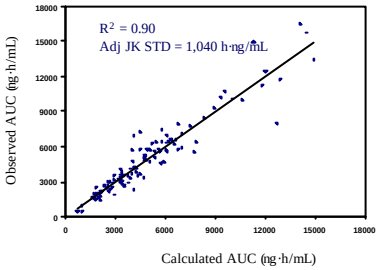
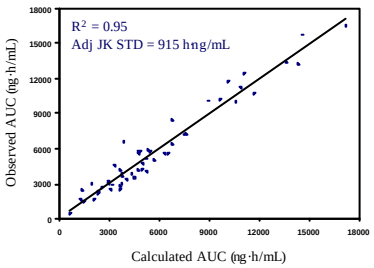


Figure 6: Calculated vs. Observed AUCs using C_0, C_1, C_2 and C_4



Correlation with C_{trough}

- C_{12h} for LPV was best correlated with the concentrations measured at 10 hours after the morning dose (R^2=0.91, Adj. JK. STD = 919) with no improvement with additional data.
- For RTV, no adequate correlation for C_{12h}emerged from the analyses

CONCLUSIONS

- LPV exposure can be accurately estimated for most patients with a single plasma concentration determined at 8 hours after an observed medication dose.
- More precise LPV AUC estimates can be made by collecting data at both 2 and 8 hours or alternatively at 0, 1, 2, and 4 hours after dosing. Data collected at these times yield good estimates of RTV exposure for these regimens.
- This method is inadequate for estimating evening trough for both LPV and RTV.

Providence HEALTH CARE Vancouver, British Columbia, Canada

British Columbia Centre *for* Excellence *in* HIV/AIDS

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