Therapeutic Drug Monitoring of Lopinavir/Ritonavir (Tablet Formulation) in Pregnancy

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BACKGROUND

- Lopinavir/ritonavir, in combination with two NRTIs, is widely used during pregnancy to reduce the risk of mother-to-child transmission of HIV
- Few pharmacokinetic data are available with the tablet formulation of lopinavir/ritonavir in pregnancy
- It remains uncertain as to whether it is necessary to increase the lopinavir/ritonavir dosage to maintain virologic control and reduce the risk of transmission

STUDY OBJECTIVES

- To explore the relationship between lopinavir/ritonavir drug concentrations and viral load during pregnancy

STUDY DESIGN

- Retrospective study of lopinavir plasma concentrations in pregnancy
- Routine samples from the Quebec Antiretroviral Therapeutic Drug Monitoring (TDM) Program were evaluated
- Collaboration with Sainte-Justine Hospital for additional information on virologic and immunologic data, outcomes of pregnancy and HIV-transmission

INCLUSION CRITERIA

- Samples from HIV-infected pregnant women on lopinavir/ritonavir 400/100 mg twice daily (tablet formulation) obtained during the third trimester
- Samples obtained between 4 and 16 hours post-dose

METHODS

- Extrapolated minimum concentrations (Cmin) were calculated for each sample (using an estimated half-life of 8.9 hours)
- Genotypic inhibitory quotients (GIQs) were calculated in patients with lopinavir-associated protease mutations
- Results were considered therapeutic if Cmin: > 1 mg/L for PI-naive patients
  > 5 mg/L for PI-experienced patients
- For patients with protease mutations, results were considered therapeutic if GIQ > 2.1 mg/L/mutation

STATISTICAL ANALYSIS

- Difference in lopinavir extrapolated Cmin between detectable and undetectable viral load (VL) was compared using the non-parametric Wilcoxon Rank Sum test
- Factors associated with lopinavir extrapolated Cmin were evaluated based on the Pearson coefficient correlation and slope from simple linear regression
- SAS version 9.1

RESULTS

PLASMA SAMPLES

- 45 plasma samples were reviewed
  - 12 excluded since time post-dose < 4 hours or > 16 hours
  - 1 excluded due to no time post-dose available
  - 7 excluded since lopinavir/ritonavir dosage of 600/150mg (among 3 women)
- 25 samples were retained from 25 women

POPULATION CHARACTERISTICS (N=25)

	Median	Range
Age (years)	33	23 – 42
Body weight (kg)	78.7	56.4 – 98.8
Height (m)	1.65	1.53 – 1.81
Time of pregnancy at the moment of TDM (weeks of gestation)	32.1	28.7 – 36.0
CD4 at time of TDM (cells/mm^3)	546	133 – 1344

	N	%
Race		
Black	19	76%
Caucasian	5	20%
Other	1	4%
Experience to protease inhibitors		
Naïve	23	92%
Unknown	2	8%
Presence of protease mutations	2	8%

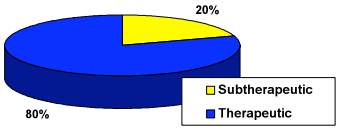
LOPINAVIR CONCENTRATIONS

	Median	Range
Time post-dose (hours)	7.58	4.50 – 16.00
Lopinavir concentration (mg/L)	3.05	0.10 – 15.85
Lopinavir extrapolated Cmin (mg/L)	2.77	0.12 – 9.74
Ritonavir concentration (mg/L)	0.07	0.01 – 1.65

CORRELATION WITH LOPINAVIR C_{min}

	Correlation coefficients	P-value	Slopes (CI)
Body weight	0.23	0.31	0.04 (-0.04, 0.11)
Height	0.24	0.26	6.9 (-5.4, 19.2)
Ritonavir concentration	0.82	< 0.0001	5.4 (3.8, 7.0)

LOPINAVIR TDM INTERPRETATIONS



- The 2 GIQs calculated were subtherapeutic (0.93 and 0.56 mg/L/mutation)

VIROLOGIC DATA

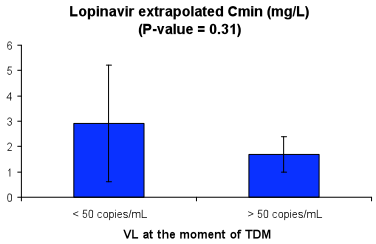
	N	%
At the moment of TDM		
VL undetectable*	22	88%
VL detectable	3	12%
At the moment of delivery**		
VL undetectable	21	87.5%
VL detectable	3	12.5%

*Minimal threshold of detection = 50 copies/mL
**1 patient has not delivered yet

RELATIONSHIP BETWEEN TDM INTERPRETATION AND VL

	N	%
Therapeutic and undetectable VL	17	68%
Therapeutic and detectable VL	3	12%
Subtherapeutic and undetectable VL	5	20%
Subtherapeutic and detectable VL	0	0%

FACTORS ASSOCIATED WITH VL



OUTCOMES OF PREGNANCY (N=24*)

	N	%
Mode of delivery		
Elective vaginal delivery	18	75%
Caesarian section	6	25%

	Median	Range
End of pregnancy (weeks of gestation)	38.71	32.43 – 41.14
Newborn's weight (grams)	3042.5	1850.0 – 3865.0

*1 patient has not delivered yet

- Out of 24 newborns for whom the transmission data were available, no case of HIV transmission was reported

DISCUSSION

- Some VL were detectable despite therapeutic levels and no subtherapeutic levels were associated with detectable VL.
- Lower lopinavir Cmin tended to be associated with a detectable VL though the difference was not statistically significant.
- Detectable VL during the third trimester or at delivery did not lead to HIV transmission to the newborn in this small sample.

CONCLUSIONS

- We observed an important proportion of subtherapeutic concentrations in women receiving the tablet formulation of lopinavir/ritonavir 400/100 mg twice daily during the third trimester of pregnancy.
- Given the small number of detectable VL, no clear relationship between lopinavir Cmin and VL could be established.
- Until further data are available, we propose to do TDM in pregnant women receiving lopinavir/ritonavir.

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