

Multiple-Dose Kaletra® (Lopinavir/ritonavir) Does Not Affect the Pharmacokinetics of the CYP2D6 Probe, Desipramine

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ABSTRACT

Background

The HIV-protease inhibitor lopinavir/ritonavir (LPV/r) at clinical conc inhibits CYP3A *in vitro* and *in vivo*, but is predicted to be a very weak inhibitor of CYP2D6 from LPV/r *in vitro* and previous ritonavir *in vivo* data. The purpose was to confirm that LPV/r 400/100 mg BID would minimally affect the pharmacokinetics (PK) of the CYP2D6 probe, desipramine (DMI).

Methods

This was an open-label sequential study in 16 healthy males and females; 15 completed the study. Subjects were given a single 100 mg dose of DMI on Day 1. LPV/r 400/100 mg BID was given on Days 6-20. A single dose of DMI 100 mg was given on Day 16. Plasma samples were collected for 120 hours after each DMI dose; LPV/r samples were obtained over 12 h on Day 16. DMI, 2-OH DMI and LPV/r were measured by LC/MS/MS; noncompartmental methods were used for PK. Effect of LPV/r on DMI was assessed by paired t-test; 90% confidence intervals (CI) for the bioavailability of the combination regimen relative to DMI alone were obtained for DMI log-transformed C_{max} and AUC.

Results

Mean $\pm$ SD, point estimates and 90% CI of C_{max} and AUC_∞ for DMI + LPV/r (Day 16) vs. DMI alone (Day 1) are below:

PK Parameter	Mean $\pm$ SD (N=15)		Relative Bioavailability* Day 16 vs. Day 1	
	Day 16	Day 1	Point Estimate	90% CI
C_{max} (ng/mL)	29.8 $\pm$ 12.5	38.8 $\pm$ 8.8	0.905	0.844 – 0.969
AUC _∞ (ng•h/mL)	1326 $\pm$ 449	1337 $\pm$ 741	1.051	0.956 – 1.156

* Based on ratio of geometric means.

The 90% CI for DMI C_{max} and AUC was within 0.80 to 1.25, suggesting no significant effect of LPV/r on DMI bioavailability. DMI half-life was similar on Days 16 and 1 (22.9 vs. 21.2 h) and T_{max} occurred slightly later during LPV/r (8.5 vs. 6.9 h, p=0.034). The 2-OH DMI metabolite C_{max} decreased by 34% (19.6 $\pm$ 8.7 vs. 29.8 $\pm$ 12.5 ng/mL, p<0.001) and AUC decreased by 25% (606 $\pm$ 197 vs. 808 $\pm$ 245 ng•h/mL, p<0.001). Since there was no effect on DMI PK, the slight reduction in 2-OH DMI AUC is likely due to induction of glucuronidation by LPV/r, rather than inhibition of CYP2D6-mediated formation from DMI. Conc of LPV/r were within the expected range.

Conclusions

Consistent with predictions, LPV/r does not inhibit CYP2D6-mediated metabolism at clinically relevant concentrations.

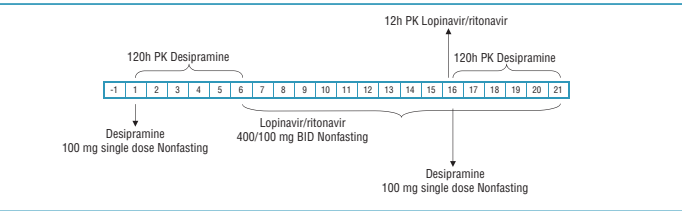
INTRODUCTION

- Kaletra® (Lopinavir/ritonavir or LPV/r) is an HIV-protease inhibitor approved in the US and Europe for treatment of HIV in combination with other antiretrovirals.
- Clinical adult dose of LPV/r is 400/100 mg BID taken with food.
- LPV/r inhibits CYP3A *in vitro* and *in vivo* at clinical concentrations.
- Based on *in vitro* data, LPV/r is predicted to be a very weak inhibitor of CYP2D6 *in vivo*.
- Desipramine (DMI) is a secondary amine tricyclic antidepressant (TCA).
- DMI is used as a probe drug to quantify inhibition of CYP2D6 metabolism *in vivo*.
- DMI is metabolized primarily by aromatic hydroxylation to 2-OH DMI *via* CYP2D6:
 - CYP2D6 is polymorphically controlled and ~5-10% of Caucasians lack this enzyme.
 - Poor metabolizers (PMs) have drastically increased concentrations (AUC) of DMI of 7- to 10-fold compared to extensive metabolizers (EMs) for any given dosage, indicating that ~85% of DMI metabolism is mediated by CYP2D6.
 - Potent CYP2D6 inhibitors such as quinidine, paroxetine and fluoxetine will reduce the clearance of DMI by 5- to 10-fold.

OBJECTIVE

To evaluate the potential for concurrent dosing of the HIV-1 protease inhibitor LPV/r to have a clinically significant effect on the pharmacokinetics of the CYP2D6 probe, desipramine.

STUDY DESIGN



Demographics

- 16 healthy adult male and female subjects were enrolled.
- Screened for CYP2D6 genotype; PMs were excluded.
- 15 subjects completed the study
 - One subject discontinued study drug prematurely due to hypertriglyceridemia.

	Mean $\pm$ SD (N=15)	Min - Max
Age (years)	35 $\pm$ 10	19 - 49
Weight (kg)	78 $\pm$ 13	61 - 98
Height (cm)	175 $\pm$ 7	163 - 189
Sex	12 Males (80%), 3 Females (20%)	
Race	12 Caucasian (80%), 2 Black (13%), 1 Hispanic (7%)	

METHODS

- CYP2D6 genotype was determined using standard polymerase chain reaction (PCR) DNA amplification techniques.
- DMI, 2-OH DMI, lopinavir (LPV) and ritonavir (RTV) plasma concentrations were determined by LC/MS/MS:
 - DMI and 2-OH DMI lower limit of quantitation (LOQ) = 0.250 ng/mL.
 - LPV and RTV LOQ = 11 ng/mL.
- Noncompartmental methods were used to determine pharmacokinetic parameters.
- Effect of LPV/r on DMI was assessed by paired t-test.
- 90% confidence intervals (CI) for the bioavailability of the combination regimen relative to DMI alone were obtained for DMI log-transformed C_{max} and AUC.

RESULTS

Figure 1. Desipramine Mean (SD) Concentration-Time Profiles

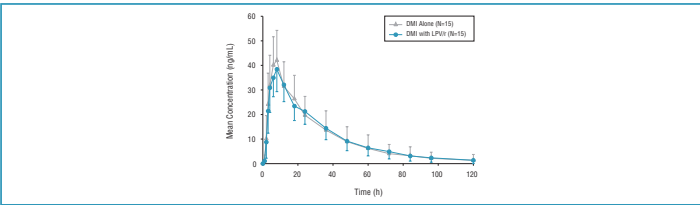


Table 1. Desipramine Pharmacokinetic Parameter Estimates

	Day 1: DMI Alone (N=15)	Day 16: DMI with LPV/r (N=15)
C_{max} (ng/mL)	43.3 $\pm$ 11.6	38.8 $\pm$ 8.8*
T_{max} (h)	6.9 $\pm$ 1.3	8.5 $\pm$ 2.4
AUC _∞ (ng•h/mL)	1268 $\pm$ 599	1269 $\pm$ 380
AUC ₀₋₁₂₀ (ng•h/mL)	1337 $\pm$ 741	1326 $\pm$ 449
$t_{1/2}$ (h)	21.2*	22.9*
CL/F (L/h)	90.3 $\pm$ 35.3	82.4 $\pm$ 23.0

Pharmacokinetic parameter estimates presented as mean $\pm$ SD
* Harmonic Mean
* Statistically significantly different from reference (Day 1, paired t-test, p < 0.05)

Table 2. Relative Bioavailability of Desipramine

Parameter	Study Day		Geometric Means		Relative Bioavailability	
	Test	Reference	Test	Reference	Point Estimate*	90% CI
C_{max}	16	1	37.9	41.9	0.905	0.844 – 0.969
AUC _∞	16	1	1221	1164	1.049	0.958 – 1.148
AUC ₀₋₁₂₀	16	1	1265	1203	1.051	0.956 – 1.156

*Based on ratio of geometric means

Figure 2. Desipramine AUC_∞

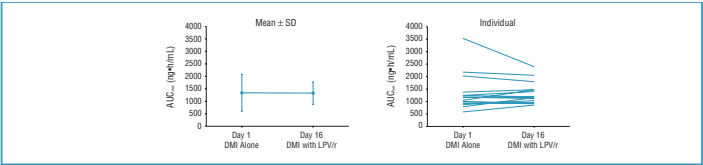


Figure 3. Desipramine C_{max}

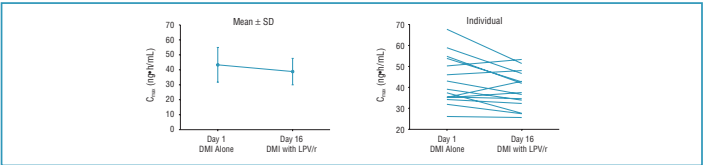


Figure 4. Desipramine $t_{1/2}$

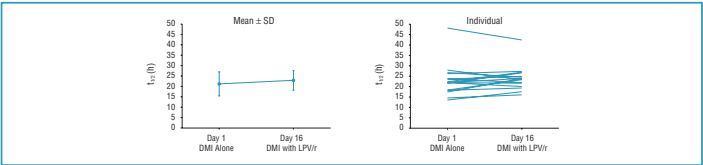


Figure 5. 2-OH Desipramine Mean (SD) Concentration-Time Profiles

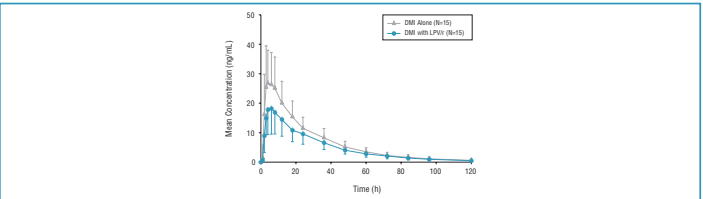


Table 3. 2-OH Desipramine Pharmacokinetic Parameter Estimates

	Day 1: DMI Alone (N=15)	Day 16: DMI with LPV/r (N=15)
C_{max} (ng/mL)	29.8 $\pm$ 12.5	19.6 $\pm$ 8.7*
T_{max} (h)	5.1 $\pm$ 2.2	5.1 $\pm$ 1.6
AUC _∞ (ng•h/mL)	781 $\pm$ 247	585 $\pm$ 195*
AUC ₀₋₁₂₀ (ng•h/mL)	808 $\pm$ 245	606 $\pm$ 197*
2-OH/Parent AUC _∞ Ratio	0.70 $\pm$ 0.26	0.50 $\pm$ 0.20
$t_{1/2}$ (h)	21.6*	22.8*

Pharmacokinetic parameter estimates presented as mean $\pm$ SD
* Harmonic Mean
* Statistically significantly different from reference (Day 1, paired t-test, p < 0.05)

Table 4. Relative Bioavailability of 2-OH Desipramine

Parameter	Study Day		Geometric Means		Relative Bioavailability	
	Test	Reference	Test	Reference	Point Estimate*	90% CI
C_{max}	16	1	18.0	27.2	0.660	0.605 – 0.720
AUC _∞	16	1	557.8	751.6	0.742	0.693 – 0.795
AUC ₀₋₁₂₀	16	1	579.1	779.8	0.743	0.693 – 0.795

*Based on ratio of geometric means

Figure 6. 2-OH Desipramine AUC_∞

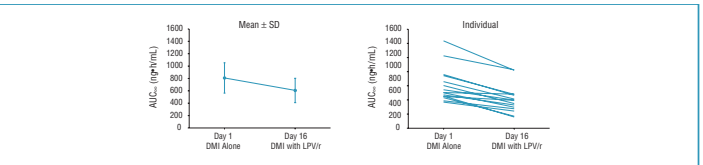


Figure 7. 2-OH Desipramine C_{max}

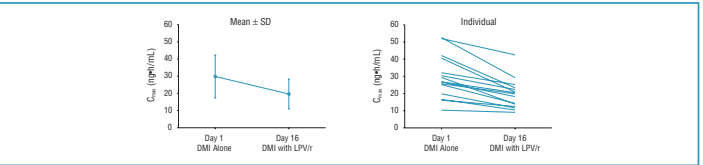


Table 5. Lopinavir and Ritonavir Pharmacokinetic Parameter Estimates

	LPV Day 16 (N=15)	RTV Day 16 (N=15)
C_{max} (µg/mL)	8.02 $\pm$ 2.23	0.810 $\pm$ 0.450
T_{max} (h)	4.8 $\pm$ 2.6	4.9 $\pm$ 2.5
C_{min} (µg/mL)	4.28 $\pm$ 2.12	0.151 $\pm$ 0.088
AUC ₀₋₁₂ (µg•h/mL)	73.7 $\pm$ 23.5	4.74 $\pm$ 2.20

Pharmacokinetic parameter estimates presented as mean $\pm$ SD

- The 90% CIs for DMI C_{max} and AUC were within 0.80 to 1.25 range.
- DMI half-life was similar on Day 16 and 1 (22.9 vs. 21.2 h).
- DMI T_{max} occurred slightly later on Day 16 than Day 1 (8.5 vs. 6.9 h, p=0.03).
- 2-OH DMI C_{max} decreased by 34% (19.6 vs. 29.8 ng/mL, p<0.001).
- 2-OH DMI AUC decreased by 25% (606 vs. 808 ng•h/mL, p<0.001).

DISCUSSION

- LPV/r had no effect on DMI bioavailability.
- The slight reduction in 2-OH DMI AUC is likely due to induction of glucuronidation by LPV/r, rather than inhibition of CYP2D6-mediated formation from DMI.
- LPV and RTV concentrations were within the expected range.

CONCLUSION

- LPV/r does not inhibit CYP2D6-mediated metabolism at clinically relevant concentrations.