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Cheri Klein
100 Abbott Park Road
Dept. AP13A-3 R4PK
Abbott Park, IL 60064-6104
Email: cheri.klein@abbott.com

Predicted Pharmacokinetics of Lopinavir after Multiple-Dose Administration of Lopinavir/Ritonavir Tablet to Pediatric Patients

W Liu[1], CE Klein[1], K Marsh[1], L Hernandez[1], BM Bernstein[1], GJ Hanna[1]
[1]Abbott Laboratories, Abbott Park, IL, USA

Background

Purpose of the Study: Lopinavir/ritonavir (LPV/r) is indicated for the treatment of HIV infection in patients > 2 yrs old. A LPV/r 200/50 mg tablet was developed which reduces pill count, offers less restrictive storage compared to the soft gelatin capsule (SGC) and may be taken without meals. Preclinical data suggest that crushing the tablet may result in lower bioavailability. The purpose of this simulation was to predict lopinavir (LPV) levels following administration of 1 or 2 intact tablets twice daily (BID) to pediatric patients.

Methods: The model was built using SGC data from pediatric patients and the tablet absorption phase from healthy adult volunteers. 1000 pediatric patients aged 2 to 16 years with body surface areas (BSA) of 0.25 to 1.7 m^2 were simulated for 1 or 2 tablets BID. The AUC_{12} was compared to the efficacious AUC_{12} in pediatric patients.

Summary of Results: The predicted average LPV AUCs are shown below.

BSA (m^2)	1 Tablet (200/50 mg) BID	2 Tablets (400/100 mg) BID
0.35 to 0.45	190.0	435.0
0.45 to 0.55	113.4	237.8
0.55 to 0.65	97.1	206.8
0.65 to 0.75	79.1	174.6
0.75 to 0.85	70.3	153.8
0.85 to 0.95	59.8	143.7
0.95 to 1.05	51.9	126.2
1.05 to 1.15	46.0	112.5
1.15 to 1.25	41.9	101.6
1.25 to 1.35	38.0	93.3
1.35 to 1.45	34.5	81.5

The average ± SD of lopinavir AUC_{12} shown to be efficacious in pediatric patients with the recommended 230/57.5 mg/m^2 BID dose of oral solution was 72.6 ± 31.1 µg•h/mL.

Conclusions: These simulations suggest that there is a limited range of pediatric BSA for which the intact tablet provides clinically appropriate LPV exposure. As the tablet should not be crushed or broken, the development of a pediatric strength tablet is warranted to provide dosing flexibility for this population.

Introduction

Lopinavir/ritonavir (LPV/r) is indicated for the treatment of HIV-1 infection in adult and pediatric populations age 2 years or greater.

Pediatric dosing of LPV/r is based on body surface area (BSA) or body weight. Optimal dosing is achieved with a dosage form (such as the oral solution) that can accommodate the spectrum of BSA or body weight encountered in this population.

- Recommendations for the SGC in Europe were developed to provide dosing (and, therefore, LPV exposure) within 20–30% of recommended dose with the oral solution, based on BSA.
- Both the oral solution and the SGC are recommended to be taken with meals to enhance bioavailability and limit pharmacokinetic variability.

A LPV/r 200/50 mg adult tablet was recently developed which reduces pill count compared to the SGC, does not require refrigeration prior to dispensing and may be taken without regard to meals.

Introduction cont.

Recent preclinical work suggests that crushing the tablet results in lower bioavailability of LPV/r and, therefore, is not recommended.

- A cross-over study was performed in beagle dogs (n=10) comparing a 200/50 mg dose as an intact tablet to one which was ground and placed in a capsule prior to dosing.
  - –Plasma concentrations determined by HPLC-MS/MS
  - –Point estimates calculated using logarithmic transformation of AUC
- The ground tablet provided significantly lower LPV and ritonavir (RTV) bioavailability.

	AUC_{24} (µg•h/mL)		
	Ground Tablet	Reference Tablet	Point Estimate
LPV	62.1 ± 9.7	90.2 ± 14.8	0.67
RTV	2.9 ± 0.5	8.5 ± 2.3	0.39

Purpose

To predict LPV levels following administration of 1 or 2 intact adult (200/50 mg) LPV/r tablets BID to pediatric patients.

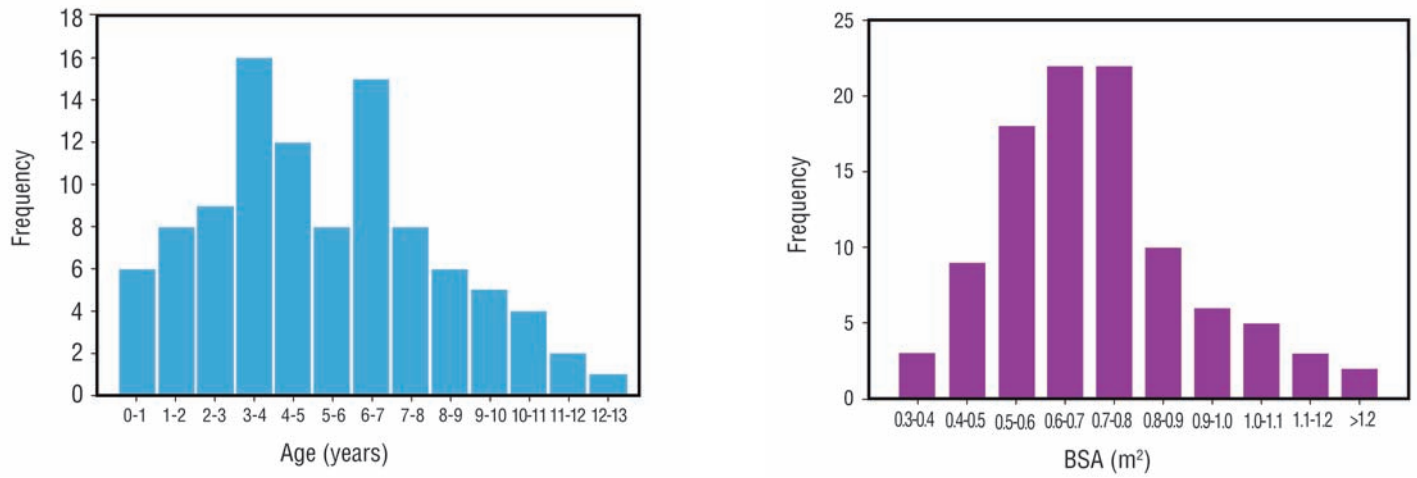
Methods

Prediction of LPV/r Oral Solution Pharmacokinetics in the Pediatric Population

Data from Study M98-940[1] were used to develop the pharmacokinetic model for LPV/r in pediatric subjects.

- Study M98-940 enrolled 100 subjects (age 6–151 months for 230/57.5 mg/m^2; 6-143 months for 300/75 mg/m^2) with 12-hour concentration profiles analyzed in 53 subjects and trough concentrations determined in all subjects.
- LPV/r oral solution was administered as 230/57.5 mg/m^2 or 300/75 mg/m^2 with or without nevirapine co-administration.
  - – LPV/r was taken with meals to enhance bioavailability and reduce pharmacokinetic variability of the oral solution.
- Demographics of M98-940 are shown in Figure 1. Prediction of LPV/r Oral Solution Pharmacokinetics in the Pediatric Population

Figure 1. Demographics of Subjects Enrolled in Study M98-940



Methods cont.

The observed pharmacokinetic parameters of LPV in the 53 children analyzed with 12-hour pharmacokinetic sampling following oral solution administration are shown in Table 1.

Table 1. Observed LPV Exposure in Children Following LPV/r Administration, Study M98-940[1]

	LPV		
	AUC_{12} (µg•h/mL)	C_{max} (µg/mL)	C_{trough} (µg/mL)
230 mg/m² BID	72.6 ± 31.1	8.16 ± 2.94	4.74 ± 2.93
300 mg/m² BID	116.4 ± 57.1	12.45 ± 5.77	7.92 ± 4.52

NONMEM v. 5 was used to estimate LPV/r pharmacokinetic parameters. The contribution of covariates such as body size (BSA or weight), sex, age and nevirapine co-administration was tested for influence on LPV and RTV pharmacokinetic parameters.

The base models for LPV and RTV were one-compartment models where the elimination of LPV was dependent on the RTV concentration.[2]

The final RTV model included the influence of age, BSA and sex on RTV volume of distribution (V_d), nevirapine co-administration on RTV elimination rate constant (K_{el}) and sex on the duration of RTV absorption from the oral solution (R_1).

The final LPV model included the influence of BSA on LPV V_d.

Prediction of LPV/r Tablet Pharmacokinetics in the Pediatric Population

LPV/r pharmacokinetic parameters and influence of covariates (with the exception of the absorption phase) were derived from the model developed with the M98-940 data.

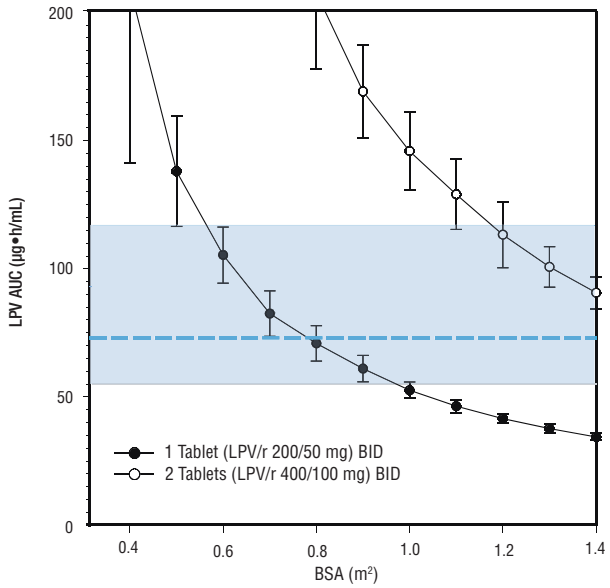
LPV/r absorption was estimated from adult bioequivalence studies of the LPV/r tablet as previously described.[3]

Clinical Trial Simulator™ software v. 2.2 (Pharsight Corp., Mountain View, CA) was used to predict the concentration-time profile of 1 or 2 adult LPV/r tablets (200/50 mg or 400/100 mg BID) in 1000 pediatric subjects age 2 to 16 years with BSA of 0.25 to 1.7 m².

Results

The average predicted LPV AUC_{12} for pediatric patients given 1 or 2 LPV/r adult tablets BID are shown in Figure 2 and described in Table 2.

Figure 2. Predicted Average ± SD LPV AUC_{12} in Pediatric Patients Receiving 1 or 2 Adult LPV/r Tablets



The shaded area represents exposure between 20% lower and 30% higher than those achieved with the standard 230/57.5 mg/m² dosing with the oral solution. The dotted line represents the average exposure achieved with the recommended dose of oral solution.

Table 2. Predicted Average LPV Exposure in Children Following LPV/v Tablet Administration by BSA

BSA (m²)	1 Tablet (200/50 mg) BID	2 Tablets (400/100 mg) BID
0.35 to 0.45	190.0	435.0
0.45 to 0.55	113.4	237.8
0.55 to 0.65	97.1	206.8
0.65 to 0.75	79.1	174.6
0.75 to 0.85	70.3	153.8
0.85 to 0.95	59.8	143.7
0.95 to 1.05	51.9	126.2
1.05 to 1.15	46.0	112.5
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1.25 to 1.35	38.0	93.3
1.35 to 1.45	34.5	81.5

Average AUC_{12} values in µg•h/mL.

Results cont.

A comparison of the predicted AUC_{12} in Table 2 to the observed AUCs in Study M98-940 (Table 1) suggests that dosing with a single 200/50 mg LPV/r tablet BID will result in exposures similar to those achieved with the currently recommended oral solution dose of 230/57.5 mg/m^2 BID in patients with BSA between 0.65m^2 and 0.85m^2.

Similarly, two 200/50 mg LPV/r tablets BID approximate the exposure achieved with the oral solution dosed at 230/57.5 mg/m^2 in patients with BSA greater than 1.35 m^2.

The predicted percentage of pediatric patients predicted to be within and outside of the preferred AUC range (20% lower to 30% higher than average exposure achieved in M98-940) is summarized in Table 3.

Table 3. Predicted Percent of Pediatric Patients Correctly Dosed when Receiving LPV/r Adult Tablets

Body Surface Area (m^2)	Twice Daily Tablet Dose	% Within Preferred Range	% Lower than Range	% Higher than Range
< 0.5	1 tablet (200/50 mg)	17	0	83
0.5 to 0.9	1 tablet (200/50 mg)	94	3	3
0.9 to 1.2	1 tablet (200/50 mg)	5	95	0
	2 tablets (400/100 mg)	32	0	68
> 1.2	2 tablets (400/100 mg)	99	0	1

Conclusions

The adult LPV/r tablet formulation provides limited flexibility to support accurate dosing for pediatric patients.

- A LPV/r tablet dose of 200/50 mg in children with BSA between 0.65 and 0.85 m^2 and a tablet dose of 400/100 mg BID in children with a BSA of more than 1.35 m^2 may provide appropriate LPV exposure.
- Dosing of the tablet in children with BSA above or below these ranges is likely to result in drug exposures that differ substantially from those achieved with the currently recommended LPV/r dose of 230/57.5 mg/m^2.

As crushing the tablet is likely to significantly reduce LPV bioavailability, the oral solution, with its inherently greater dosing flexibility, should be the preferred formulation for use in children.

The development of a pediatric strength tablet is warranted to enhance utility of LPV/r in this population and is underway.

References

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2. Hsu A, et al., Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis Volume III, 2004.
3. Zhu, et al. Modeling the Drug Interaction of Lopinavir/Ritonavir with Efavirenz. Poster 78 presented at: ASCPT; 2006.