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Pharmacokinetics of Unboosted Atazanavir in Treatment-Experienced HIV-infected Children, Adolescents and Young Adults

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Abstract

HIV protease inhibitor use in pediatrics is challenging due to the poor palatability and/or toxicity of concomitant low-dose ritonavir. Atazanavir without ritonavir (unboosted) is not recommended for patients with prior virologic failure; a common problem for perinatally-infected adolescents. Atazanavir 400 mg once-daily provided suboptimal exposure. Higher unboosted doses or splitting the daily dose to twice-daily warrants investigation in this treatment-experienced population.

Keywords

Pharmacokinetics; antiretrovirals; atazanavir; pediatrics

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Introduction

Perinatally HIV-infected adolescents often receive complex antiretroviral (ARV) regimens due to prior treatment failures. Yet, the addition of ritonavir to many of these regimens [1], increases the adverse-events rate and substantial number of patients often refuse it because of its poor palatability. Unboosted atazanavir (uATV) is FDA-approved for treatment-of naive adolescents ≥13 years and weighing >39 kg but is not recommended for treatment-experienced patients (1–3). Despite this lack of approval, unboosted atazanavir is sometimes used in heavily treatment-experienced populations due to the intolerability of ritonavir and lack of other alternatives. We investigated the pharmacokinetics (PK) of unboosted atazanavir given once-daily in treatment experienced children, adolescents, and young adults.

Methods

The International Maternal Pediatric and Adolescent AIDS Clinical Trial (IMPAACT) protocol P1058A was a multi-center trial studying the pharmacokinetics of common antiretroviral combinations in children, adolescents and young adults in the United States (clinicaltrials.gov, NCT00977756). The design was opportunistic in that the ARVs under study were prescribed by their clinician as part of standard clinical care. Eligible subjects included HIV-infected patients age 6 to <24 years old, with a body surface area ≥0.85 m^2, and on a stable ARV regimen of interest for at least 30 days; in the current study this included regimens that contained ATV 400 mg or 600 mg once daily (QD). All patients received ATV and optimal background regimens at their physician's discretion. Subjects were excluded if they had clinical or laboratory toxicity that was grade ≥2 (grade >1 for total bilirubin) according to the Division of AIDS table for grading the severity of adverse events (http://rcc.tech-res-intl.com/) at screening or a hemoglobin level of <8.5 g/dL. A negative pregnancy test was required at enrollment for females of child bearing capacity. Plasma HIV-1 RNA level and CD4 cell counts were collected as part of routine care. This study was approved by the Institutional Review Board at each participating site.

On the day of pharmacokinetic evaluation, ARV drugs were administered in an observed, open-label fashion with food (full meal or light snack, high or low fat). Blood samples were collected pre-dose and at 1, 2, 4, 6, 8, 12 and 24 hours post-dose. Plasma samples were stored at −70°C until analysis. Atazanavir concentrations were measured using a validated ultra-performance liquid chromatography coupled with tandem-mass spectrometry assay. The assay was validated according to the FDA guidance over the range 0.010–15 mg/L. Overall interassay/intraassay variability was <20% at the lower limit of quantification and <15% at other concentrations. The laboratory participates in the clinical pharmacology quality assurance (CPQA) external quality control program support by the DAIDS, NIH. Atazanavir pharmacokinetic parameters were determined using a non-compartmental analysis (WinNonlin Phoenix v6.30.395, Pharsight Corp., CA). Using an estimate of the coefficient of variation (CV) in area under concentration time curve ($AUC_{0–24}$) reported in P1020A (CV=50%), we determined that a sample of size 25 would provide 80% power to detect a augmentation or diminution of exposure (as measured by $AUC_{0–24}$) of at least 30% relative to the reference mean, using a one-sample, two-sided test with 5% Type I error (4).

The 90% confidence intervals (90% CI) for the geometric mean (GM) of ATV pharmacokinetic parameters [$AUC_{0–24}$, maximum concentration (Cmax), 24-hour post dose concentration (C_{24})] were compared with adult target ranges (2). Associations between baseline characteristics at study entry and ATV PK parameters were assessed using a linear regression model.

Results

Twenty-six HIV-infected patients were enrolled. Three subjects were excluded; 2 did not have blood sampling performed for PK assessment and one received ATV 450 mg QD. Eighteen subjects (8 males) received ATV 400 mg QD: 14 African American, 1 White and 3 Hispanic, with tanner stages 1 (n=1), 3 (n=1), and 5 (n=16). Their median (range) age was 20.3 (6–23) years, weight 70 (22–111) kg, body surface area 1.79 (0.85–2.29) m^2, HIV-1 RNA viral load <40 (<40–125,080) copies/mL (82% <200 copies/mL), and CD4 cell count 588 (21–1171) cells/μL. Among the five subjects (4 males) receiving ATV 600 mg QD,4 were African Americans and 1 Hispanic, with Tanner stage 3 (n=1), 4 (n=1) and 5 (n=3); median age was 16.9 (13–23) years, weight 65 (45–86) kg, body surface area 1.72 (1.43–2.1) m^2, HIV-1 RNA viral load <40 (<40–1120) copies/mL (80% <200 copies/mL), and CD4 cell count 819 (656–1026) cells/μL. One subject receiving ATV 400 mg QD had a dose increase to 600 mg QD and had PK sampling repeated.

The pharmacokinetic parameters of ATV are summarized in Table 1. Both the AUC_{24} and the C_{max} were higher in subjects receiving the 600 mg QD compared to those with 400 mg. Six subjects (39%) had a C_{24} below 0.15 mg/L (suggested minimum threshold (5) with ATV 400 mg and 2 subjects (33%) with ATV 600 mg QD. Multivariate analysis suggested that body weight (p=0.001) was independently associated with atazanavir AUC_{24} and C_{24}, after adjusting for dose. A similar association was observed for BSA (p=0.003). No associations between age, sex and CD4 cell count and ATV PK parameters were identified.

Discussion

In the current study atazanavir 400 mg QD provided comparable $AUC_{0–24}$, Cmax and C_{24} values to those achieved in adults with unboosted atazanavir. As expected, the ATV AUC and Cmax were higher with the 600 mg QD dose but the C_{24} was lower with the higher dose. Nevertheless, the AUCs and C_{24} of both unboosted regimens fell well below those achieved with ATV/r. While the GM ATV trough concentration (C_{24}) was at least 120-fold times higher than the *in vitro* 50% effective concentration (EC_{50}) of ATV (0.00141 mg/L) for wild-type (2), it was much closer to the protein-binding adjusted EC_{90} (0.014 mg/L). The effect of protein binding should be taken into account, especially in treatment-experienced subjects, when determining the EC_{50} or the EC_{90} *in vivo* for a drug like ATV which is more than 90% bound to plasma proteins. Thus, the C_{24} levels found in our study suggest that unboosted ATV once daily too often provides suboptimal concentrations for a majority of subjects. The median ATV dose in our study was 224 (175–471) mg/m^2 for the subjects receiving 400 mg and 349 (286–420) mg/m^2 for subjects receiving 600 mg QD. These mg/m^2 doses are significantly lower than those used in P1020A, where a ATV doses of 520 mg/m^2 in patients aged >2 to 13 years old and 620 mg/m^2 >13 to 21 years old satisfied

protocol-defined pharmacokinetic criteria (based on ATV targets achieved in adults receiving ATV/r). Forty-three percent of ARV-experienced children in P1020A achieved a HIV-1 RNA viral load <400 copies/mL at 48 weeks, with no difference between ATV and ATV/r (6). However, it must be noted that in P1020, the pharmacokinetic targets led to equivalent ATV exposure for unboosted and ritonavir boosted doses, which is not the case for adults where ATV exposure is 3- to 4-fold higher with ritonavir boost compared to non-boosted ATV (7) [and was reported to result in better virologic outcomes (8). The authors correctly highlight that the approved unboosted ATV 400 mg dose may not be sufficient to maintain adequate plasma concentrations, particularly for adolescents for which higher ATV oral clearance was observed, and, who frequently have difficulty with adhering to a strict medication schedule. It was suggested that an unboosted ATV daily dose of 900 mg would be required for subjects >13 years old and 475 mg for subjects 6–13 years old. Our data support the need for a much higher dose than is currently recommended as both the ATV 400 and 600 mg dose in our study produced exposures in adolescents and young adults below those achieved with ATV/r that achieve a good virologic response in adults (9). The impact of higher unboosted doses on the virologic efficacy in this heavily treated group is difficult to extrapolate but the safety data reported with higher ATV exposure in these children and adolescents are reassuring (6). However, the fact that more than a third of our subjects had a C_{24} below 0.15 mg/L, (the proposed trough concentration cut-off for virologic efficacy) and the substantial individual variability are of concern despite the fact that unboosted ATV has been licensed at a once-daily dose for treatment-naïve patients. A single nucleotide polymorphism in the pregnane X receptor has been associated with ATV C_{24} (10) and may help explain a portion of the high interpatient variability observed but host genetics data were not available in the present study. Several other studies concluded that splitting the atazanavir dose (i.e., 200 mg twice daily) resulted in higher proportion of subjects achieving C_{24} above the efficacy cut-off and better virological successes (11).

The role unboosted ATV could play in treatment regimens for experienced adolescents who cannot tolerate ritonavir remains to be determined but if a once daily dose is chosen to be used, therapeutic drug monitoring (TDM) is needed to assure acceptable trough concentrations. If TDM is not available, splitting the dose to twice-daily administration is an acceptable alternative option but more data are needed. Close viral load monitoring to avoid development of drug-resistance and improving patient's compliance are important to reduce treatment failure. The role of higher unboosted ATV doses in treatment-experienced adolescents and young adults deserves further study.

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Table 1

Pharmacokinetic parameters of atazanavir 400 mg and 600 mg once daily in children, adolescents and young adults.

	IMPAACT P1058A (GM, 95% CI)		REYATAZ® (Package Insert)* GM(CV%)	
	ATV 400 mg QD	**ATV 600 mg QD#**	**ATV 400 mg QD**	**ATV/r 300/100 mg QD**
N	18	6	13	10
AUC_{24} (mg.hr/L)	19.9 (14.1–28.1)	29.3 (13.7–62.9)	14.9 (91)	46.1 (66)
C_{max} (mg/L)	2.6 (1.8–3.7)	4.0 (1.9–8.1)	2.3 (71)	4.4 (58)
C_{24} (mg/L)	0.18 (0.09–0.36)	0.13 (0.03–0.61)	0.12 (109)	0.64 (97)
CL/F (L/hr)	20.1 (14.2–28.5)	20.5 (9.5–44.0)	NA	NA

#1 subject received ATV 400 mg and had a dose increase to ATV 600 mg and PK sampling