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Steady-state pharmacokinetics of lopinavir plus ritonavir when administered under different meal conditions in HIV-infected Ugandan adults

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Abstract

We investigated the effect of food on the steady-state pharmacokinetics of lopinavir and ritonavir in 12 Ugandan patients receiving lopinavir co-formulated with ritonavir (LPV/r) tablets using a cross-over design. Intensive pharmacokinetic sampling was performed seven days apart following LPV/r dosing under moderate fat, high fat and fasted meal conditions. Lopinavir and ritonavir concentrations were determined by liquid chromatography and tandem mass spectrometry. Compared to the fasted state, a high fat meal reduced lopinavir and ritonavir area under the curve (AUC) by 14% and 29%, respectively. With a moderate fat meal, AUC for both drugs was similar to the fasted state.

Introduction

Human immunodeficiency virus (HIV) infection disproportionately affects the poorest parts of the world.[1] Food insufficiency affects up to a third of the population in sub-Saharan Africa, where nearly 70% of all HIV infections occur.[2-3] Life-long treatment with a combination of antiretroviral drugs is the only therapeutic intervention with proven efficacy against HIV infection.[4] Standard management of HIV in adults involves daily administration of a combination of orally administered drugs. However, food intake around the time of

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drug dosing may alter the bioavailability of orally administered drugs.[5] With limited access to food, patients may consume meals less frequently than the prescribed dosing schedule for their medication. Consequently, antiretroviral drugs which can be administered without food are preferred.[6]

Lopinavir co-formulated with ritonavir (LPV/r) is the most widely used HIV protease inhibitor in resource-limited settings. Initially, LPV/r was developed as a soft elastic capsule formulation which required refrigeration for storage and food intake for optimal absorption.[7] The capsule formulation was subsequently replaced by a film-coated tablet which does not require refrigeration. In manufacturer initiated studies with single doses of LPV/r, a trend to a reduced food effect was seen with the tablets compared with the capsules. Consequently, the manufacturer recommends that LPV/r tablets can be administered without regard to meals.[8,9]

However, the effect of food on steady-state pharmacokinetics of lopinavir and ritonavir has not been studied. Furthermore, no formal evaluations have been conducted in African settings using local meals. The present study compared the steady-state pharmacokinetics of lopinavir and ritonavir in Ugandan HIV-infected patients when administered as LPV/r tablets in the fasted state versus administration with a Ugandan moderate fat meal or a Western high fat meal.

Methods

Ethics and regulatory approval

Ethics committee approval was obtained from the National AIDS Research Committee (ARC 100). The study was approved by the Uganda National Council for Science and Technology (HS 730) and registered on www.pactr.org (PACTR2010030001953121).

Study design

This was an open-label, three-phase, cross-over pharmacokinetic study. Enrolled patients were scheduled for intensive pharmacokinetic sampling on three occasions seven days apart (Day 1, Day 8 and Day 15). Assuming a t-distribution of the data, a coefficient of variation of 5% and at an alpha level of ≤0.05, 12 patients were calculated to have 80% probability to detect a 20% difference in the mean AUC of lopinavir between the fasted and either the moderate fat or the high fat meal.

Patients

Patients were enrolled if they provided written informed consent, were aged between 18 and 65 years, were stable on a LPV/r containing antiretroviral regimen for at least 12 months prior to enrolment (most recent HIV-1 RNA performed over preceding 12 months measuring below 400 copies/mL) and had no recent use of medications (including traditional medicines) known to interfere with cytochrome P450 (CYP) metabolism. Patients were excluded if they were anaemic or if they had evidence of derangement in renal function (serum creatinine above 300 μmol/L) or hepatic function (alanine transaminase elevations greater than five times the upper limit of normal). Patients were excluded if they had severe intercurrent illnesses, vomiting or diarrhoea or if they were unable to adhere to the meal sequence prescribed in the study. Pregnant women were excluded from the study.

Pharmacokinetic sampling

Patients received LPV/r tablets (Aluvia®, Abbott GmbH & Co. KG, Knollstrasse, Germany) twice daily as part of their antiretroviral regimen throughout the study. On Day 1, patients received a moderate fat Ugandan meal (665 Kcal, 20 g fat) comprising local banana

(*matooke*) cooked with onions, tomatoes and oil and tea without milk. Two adult strength tablets of LPV/r were administered less than 30 minutes after the starting and completing of the meal.

On Day 8, LPV/r was administered with a standardized high fat Western breakfast (840 Kcal, 36g fat) comprising bread, margarine, sausages and tea with milk. On Day 15, LPV/r tablets were administered to patients in the fasted state. Patients were advised to withhold food intake for 8 hours prior to LPV/r dosing and food intake was permitted four hours after administration of LPV/r. On each sampling occasion, venous samples were collected pre-dose and 1, 2, 4, 6, 8, 10 and 12 hours post-LPV/r. Plasma samples were obtained by centrifugation at the Makerere University–Johns Hopkins University Laboratory and stored at −70°C until shipment.

Determination of lopinavir and ritonavir

Lopinavir and ritonavir concentrations in plasma were determined at the University of Liverpool by a validated high performance liquid chromatography with tandem mass spectrometry method.[10] The lower limit of quantification for lopinavir and ritonavir were 8.3 and 2.5 ng/mL, respectively. For lopinavir and ritonavir, assay accuracy ranged from 91.1-106.7% and 89.5 −104.9%, respectively. Coefficient of variation (CV) was ≤ 7.1% for lopinavir and ≤ 7.6% for ritonavir at all quality control levels.

Safety assessments

Adverse events were evaluated using patient questionnaires

Data analysis

Pharmacokinetic parameters including maximal concentrations (C_{max}), time to maximal concentration (T_{max}) and concentrations 12 hours post-dosing (C_{12}) were obtained from the data. Half-life ($t_{1/2}$) and area under the concentration-time curve (AUC_{0-12}) were calculated by non-compartmental methods (WinNonlin® Version 5.2, Pharsight, MountainView, CA). Fasted data (Day 15) was used as the reference to facilitate comparison of food effects with results of the manufacturer-initiated single-dose study.[8] Geometric means (GM), geometric mean ratios (GMRs) and confidence intervals (CI) were calculated for the pharmacokinetic parameters of lopinavir and ritonavir. A food effect was assumed if the 90% CI for GMRs between fed and fasted treatments was not contained in the equivalence limits of 80-125% for either AUC_{0-12} or C_{max}. Statistical comparisons of the derived pharmacokinetic parameters (moderate fat or high fat versus fasted) were performed using the Wilcoxon signed-rank. P values ≤0.05 were considered statistically significant. Lopinavir C_{12} was interpreted using a minimum effective concentration (MEC) of 1,000 ng/mL.[11]

Results

Patients

Thirteen patients were enrolled into the study. One patient was discontinued on the first sampling visit due to cannulation difficulties and no pharmacokinetic data are available. The remaining 12 patients (six female) completed all phases of the study. The median (interquartile range) age and weight of patients was 48 (44 – 49) years and 62 (59-68) kg. Eleven patients received zidovudine plus didanosine while one patient received tenofovir plus lamivudine. For opportunistic infection prophylaxis, 11 patients used cotrimoxazole and one patient was on dapsone.

Pharmacokinetics

Lopinavir and ritonavir pharmacokinetic parameters are summarized in Table 1. Lopinavir T_{max} (median, interquartile range) was 3 (3 – 4) hours in the fasted state and 4 (4 – 6) hours and 4 (4 – 6) hours with moderate and high fat meals respectively. Similarly, ritonavir T_{max} was 3 (2 – 4) hours in the fasted state and 4 (4 – 6) hours and 4 (4 – 6) hours with moderate and high fat meals respectively.

Lopinavir $AUC_{0\text{-}12}$ and C_{max} were lower by 14% (GMR, 90% CI: 0.86, 0.77-0.95) and 14% (0.86, 0.81-0.92), respectively during administration with a high fat meal compared to the fasted state. Similarly, a 29% significant decrease in ritonavir parameters was observed for $AUC_{0\text{-}12}$ (GMR, 90% CI: 0.71, 0.61-0.84) and C_{max} (0.71, 0.60-0.84) with a high fat meal compared to the fasted state. However, compared to the fasted state, administration with a moderate fat meal yielded identical lopinavir and ritonavir $AUC_{0\text{-}12}$ and C_{max} results. Figure 1 shows individual curves for C_{max} , C_{12} and $AUC_{0\text{-}12}$ for lopinavir and ritonavir under fasted and high fat meal conditions. Under all meal conditions, lopinavir C_{12} measured above 1,000 ng/mL in all patients.

Safety assessments

No adverse events were reported.

Discussion

Ritonavir exposure parameters ($AUC_{0\text{-}12}$ and C_{max}) were 29% lower during administration with a high fat meal. This contrasts with a previously conducted single-dose study in which Klein and colleagues found no difference in the pharmacokinetics of ritonavir under fasting, moderate fat or high fat meal conditions.[8] Similarly, in the present study, lopinavir exposure was significantly reduced by a high fat meal, albeit to a milder degree than ritonavir. In comparison, the single-dose study reported increases of 26% and 19% in lopinavir $AUC_{0\text{-}12}$ with a moderate fat and high fat meal, respectively compared to fasted state.[12] The reasons for the contradictory findings between single-dose and steady-state studies are unclear, but may relate to the physicochemical characteristics of the tablet formulation and time-dependent metabolism of the study drugs.

In this study, lopinavir and ritonavir peak concentrations were observed to be delayed during LPV/r dosing with food. Slower absorption during co-administration with the moderate fat and high fat meals may have contributed to reduced lopinavir peak/trough deviation and longer lopinavir $t_{1/2}$ (as a result of ongoing absorption during the elimination phase). Lopinavir and ritonavir are hydrophobic compounds which are practically insoluble in water. However, some excipients of the film coated tablets are hydrophilic and fat could interfere with tablet dissolution and impair the release of the active pharmaceutical ingredients.[8] A high fat meal could therefore impair liberation of lopinavir and ritonavir and reduce the bioavailability of these compounds. However, while this explains how fat may reduce drug exposure, it does not explain the absence of a food effect in the prior single-dose study. The fat content of meals used in our study differed from the single-dose study. The moderate fat meal had approximately 30% more fat while the high fat meal had approximately 50% less fat than the corresponding meals used in that study. It is not clear if this could have contributed to the conflicting findings in the two studies with regard to LPV/r dosing with a high fat meal.

Lopinavir and ritonavir are metabolised by CYP3A, an enzyme which exhibits time-dependent changes in its activity. Among adults treated with LPV/r, Wyen and colleagues reported greater intestinal CYP3A activity at steady-state compared to CYP3A activity measured at a single dose of LPV/r.[13] It is therefore possible that enhanced metabolism of

lopinavir and/or ritonavir by CYP3A in the intestine at steady-state could reveal food effects that were unapparent with a single dose. However, LPV/r induces other drug metabolizing pathways at steady-state which could also contribute to the study findings.[14] Further studies are therefore needed to elucidate the mechanism for the food effect at steady-state.

Given that LPV/r is often the only protease inhibitor available in developing countries, it is important that this drug is used optimally. Under all meal conditions studied, lopinavir trough concentrations exceeded the recommended MEC for lopinavir and the mild differences under different meal conditions are unlikely to be clinically significant. Extensive evaluations of different meals were impractical so one commonly consumed staple (*matooke*) was selected while a Western high fat breakfast was used to reflect increasing adoption of Western diets in urban parts of Uganda. Thus, the study meals differed in food type as well as fat content and it is possible that food components in one meal could have influenced the results independent of the effect of fat.

In conclusion, high fat food intake led to modest reductions in ritonavir and lopinavir exposure compared to the fasted state but this is not considered to be clinically significant given that lopinavir concentrations at the end of the dosing intervals remained above the target concentration. Consequently, LPV/r tablets can be taken without regard to meals in this population. However, given that lopinavir and ritonavir pharmacokinetic parameters (AUC and C_{max}) were reduced by a high fat meal, a finding not seen in the previously conducted single-dose study, consideration should be given to the optimal design of food effect studies.

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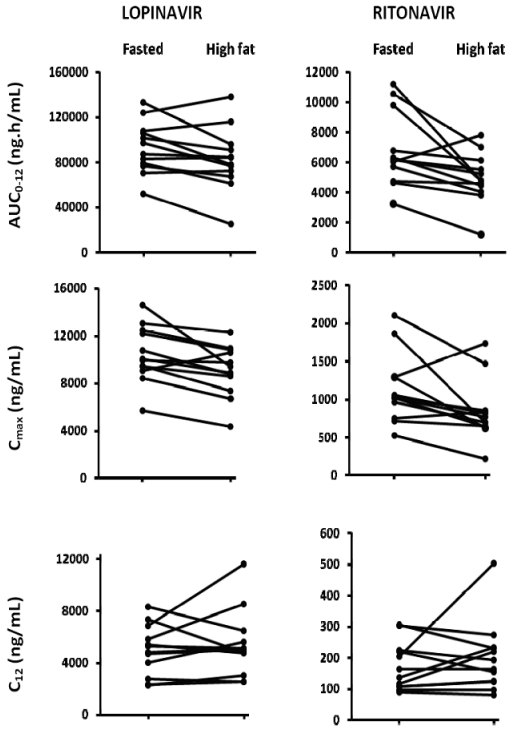

Figure 1. Individual pharmacokinetic parameters for lopinavir and ritonavir when administered in the fasted state and with a high fat meal.

Abbreviations: C_{max}, maximal plasma concentration; C_{12}, concentrations 12 hours post-dosing; $AUC_{0\text{-}12}$, area under the curve from 0 to 12 hours.

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Table 1

Lopinavir and ritonavir pharmacokinetic parameters under various meal conditions.

	Geometric mean (95% CI)			*GMR (90% CI)*	
	Fasted (Reference)	**Moderate fat**	**High fat**	***Moderate fat / Fasted***	***High fat / Fasted***
Lopinavir					
C_{max} (ng/mL)	10165 (9139-11732)	9905 (8738-11733)	8747 (7856-10209)	0.97(0.90-1.06)	**0.86 (0.81-0.92)**
AUC_{0-12} (ng.h/mL)	90275 (80513-105526)	89047 (76614-110993)	77201 (67337-97687)	0.99 (0.90-1.08)	**0.86 (0.77-0.95)**
C_{12} (ng/mL)	4607 (3931-6054)	5563 (4553-7895)	4932 (4026-6818)	1.21 (1.05-1.40)	1.07(0.95-1.21)
$t_{1/2}$ (h)	7.4 (6.4-9.0)	9.2 (8.0-11.8)	10.8 (8.6-15.9)	**1.25 (1.11-1.41)**	**1.46 (1.25 -1.71)**
Ritonavir					
C_{max} (ng/mL)	1059 (887-1383)	1078 (961-1272)	749 (616-1051)	1.02 (0.87-1.19)	**0.71 (0.60-0.84)**
AUC_{0-12} ng.h/mL)	6382 (5434-8102)	6274 (5425-7901)	4560 (4026-5850)	0.98(0.86-1.12)	**0.71 (0.61-0.84)**
C_{12} (ng/mL)	157 (130-214)	201 (165-284)	177 (138-261)	**1.28 (1.12-1.45)**	1.12 (0.94-1.33)
$t_{1/2}$ (h)	4.3 (3.9-4.8)	3.5 (3.2-3.9)	4.2 (3.7-5.2)	**0.82 (0.75-0.90)**	1.00 (0.86-1.15)

NOTE: Bold type indicates statistically significant (Wilcoxon sign-rank test) change in pharmacokinetic parameters compared to corresponding parameters in fasted state.

P values for C_{max}, AUC0-12, C12 and t1/2, respectively:

[1]Lopinavir: Moderate fat versus fasted – 0.43, 0.53, 0.07 and 0.03; High fat versus fasted – 0.01, 0.05, 0.43, 0.01.

[2]Ritonavir: Moderate fat versus fasted – 1.00, 0.53, 0.01 and 0.01; High fat versus fasted – 0.03, 0.01, 0.63, 0.93.

Abbreviations: GMR, geometric mean ratio; CI, confidence intervals, C_{max}, maximum concentration; C_{12}, concentration 12 hours post-dosing; AUC_{0-12}, area under the concentration-time curve.