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The pharmacokinetics of lopinavir/ritonavir when given with isoniazid in South African HIV-infected individuals.

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Summary

Isoniazid preventive therapy is recommended in patients on antiretroviral therapy with latent tuberculosis infection to prevent progression to active tuberculosis disease. Isoniazid inhibits CYP3A4, which metabolizes lopinavir. Administration of isoniazid may cause higher lopinavir concentrations which may increase lopinavir toxicity. Lopinavir bioavailability is increased by co-formulated ritonavir which may enhance the interaction of isoniazid on lopinavir. We studied the effect of isoniazid on lopinavir concentrations by administering isoniazid for 7 days and performing intensive pharmacokinetic sampling in 16 HIV-infected patients established on lopinavir/ritonavir-based antiretroviral therapy. Isoniazid did not significantly increase steady-state lopinavir AUC_{0–12}.

Keywords

Isoniazid; lopinavir/ritonavir; drug interactions; HIV

Brief report

Isoniazid preventive therapy (IPT) reduces the incidence of tuberculosis in HIV-infected patients on antiretroviral therapy (ART).[1] Isoniazid inhibits various cytochrome P450 (CYP) isoforms, including CYP3A4.[2] Nevirapine is metabolized to some extent by the CYP3A isoenzyme, but co-administration with isoniazid does not lead to a clinically significant increase in nevirapine concentrations.[3] Lopinavir/ritonavir is used as part of second-line ART and is metabolized by CYP3A4.[4] The effect of isoniazid on ritonavir-boosted lopinavir concentrations is unknown. The significant inhibitory effect of ritonavir on lopinavir metabolism will be present simultaneously with any potential effect of isoniazid.

We studied the interaction between lopinavir/ritonavir and isoniazid in healthy HIV-infected adults established on a lopinavir/ritonavir-based ART regimen. Isoniazid was given for 7 days and intensive pharmacokinetic sampling of lopinavir was performed before and after isoniazid therapy. Exclusion criteria were excessive alcohol consumption (in excess of 2

units per day or 14 units per week); chronic hepatic or gastrointestinal disease; taking drugs other than the study drugs known to alter the pharmacokinetics of lopinavir/ritonavir; suspected tuberculosis; isoniazid allergy and pregnancy. The study was approved by the University of Cape Town Human Research Ethics Committee and written informed consent was obtained from each participant.

Intensive pharmacokinetic sampling was performed at baseline (day 0) and repeated 7 days after isoniazid administration (day 7). Participants were admitted the night before intensive pharmacokinetic sampling. The evening and morning dose of lopinavir/ritonavir dose 400mg/100 mg (Aluvia® Abbott tablets) was observed during admission and given 12 hours apart. Blood samples were collected pre-dose in the morning and at 1 h, 2 h, 4 h, 6 h, 8 h and 12 h after the observed morning dose. Standardised meals were given between the 1 h and 2 h, the 4 h and 6 h, and 8 h and 12 h sampling times respectively. On discharge after the first intensive pharmacokinetic sampling, participants received isoniazid 5 mg/kg/day (maximum dose of 300 mg) and pyridoxine 25 mg/day both for 7 days. Intensive pharmacokinetic procedures of day 0 were repeated on day 7. Isoniazid dosing on day 7 was observed. At day 7 isoniazid is expected to be at steady-state and the potential inhibition effect on lopinavir/ritonavir maximal.

Within 1 hour of sampling, the blood samples were centrifuged, aliquoted and stored at -80°C until determination of drug concentration. We used validated liquid chromatography tandem mass spectrometry (LC/MS-MS) to determine the lopinavir and ritonavir concentrations in the plasma samples. The lower limits of quantification were: lopinavir 156 ng/ml and ritonavir 39.1 ng/ml. Inter- and intra-day coefficients of variation were below 10%. The laboratory subscribes to the National Institute of Allergies and Infectious Diseases Division of AIDS Clinical Pharmacology Quality Assurance Antiretroviral Proficiency Testing Program.

We calculated that we required 16 participants to detect a 30% increase in steady-state AUC_{0-12} with a 5% significance and 80% power by using published local data.[5] Stata version 11.0 (Stata Corporation, College Station, Texas) was used to characterize the pharmacokinetic parameters using non-compartmental analyses. The area under the plasma concentration-time curve (AUC_{0-12}) at steady-state was calculated for the 12 h dosing interval using the linear trapezoidal rule. Numerical data that followed a non-normal distribution were described using median and interquartile range (IQR), and the Wilcoxon signed-rank test was used for hypothesis testing.

We enrolled 16 participants in the study (14 female, 16 black African). The median (IQR) of the baseline characteristics were: age 34 (32 – 38), body mass index 26 (22.2 – 29) and CD4-count 677 (450 – 943) cells/mm³. Fourteen participants had viral loads of < 400 copies/ml. Isoniazid non-significantly increased the median lopinavir AUC_{0-12} at steady-state by 5% with a geometric mean ratio of 1.05 and 90% confidence interval of (0.95 – 1.16). See table 1 and figures 1 and 2 for lopinavir pharmacokinetic measures at day 0 and day 7 respectively. The pharmacokinetics of ritonavir was not significantly different at day 7 from day 0 (see table 1).

We studied the effect of isoniazid on the pharmacokinetics of lopinavir/ritonavir. We found that isoniazid did not increase the concentrations of lopinavir or ritonavir significantly at steady-state. CYP3A4 and p-glycoprotein are significantly inhibited by ritonavir in patients receiving lopinavir/ritonavir ART.[6] Isoniazid inhibition does not appear to add to the potent inhibition effect of ritonavir on lopinavir. Our study findings are limited by the short duration of the study. However inhibition of CYP occurs rapidly and it is unlikely that our findings would have been different in a longer duration trial.

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Figure 1:
Median and interquartile lopinavir concentrations over time when administered with and without isoniazid.

Figure 2:
Raw lopinavir concentration profiles over time when administered with and without isoniazid.

Table 1:

Steady-state lopinavir and ritonavir pharmacokinetic parameters before and after isoniazid administration.

	Day 0 Without isoniazid	Day 7 With isoniazid	P-value
Lopinavir pharmacokinetic parameters			
C ₀ (IQR) mg/l	9.0 (7.5 – 11.9)	8.7 (7.0 – 11.2)	0.81
C ₁₂ (IQR) mg/l	6.8 (5.1 – 10.4)	7.5 (5.5 – 11.2)	0.55
AUC _{0–12} (IQR) mg.h/l	122.9 (100.9 – 150.4)	141.1 (108.9 – 163.1)	0.41
C _{max} (IQR) mg/l	13.7 (12.0 – 16.1)	15.5 (13.6 – 17.5)	0.47
T _{max} (IQR) h	4 (2 – 4)	4 (4 – 6)	0.05
T _{1/2} (IQR) h	9.8 (6.4 – 13.5)	10.6 (5.6 – 15.1)	0.5
Ritonavir pharmacokinetic parameters			
C ₀ (IQR) mg/l	0.40 (0.28 – 0.48)	0.40 (0.26 – 0.46)	0.33
C ₁₂ (IQR) mg/l	0.23 (0.15 – 0.33)	0.22 (0.18 – 0.37)	0.62
AUC _{0–12} (IQR) mg.h/l	7.17 (5.4 – 10.1)	7.3 (5.9 – 9.4)	0.81
C _{max} (IQR) mg/l	1.2 (0.87 – 1.54)	1.2 (0.81 – 1.35)	0.51
T _{max} (IQR) h	4 (2 – 6)	3 (2 – 4)	0.26
T _{1/2} (IQR) h	3.91 (3.28 – 4.24)	4.15 (3.43 – 4.53)	0.61

IQR = median (interquartile range); C₀ = trough concentration at the start of the dosing interval; C₁₂ = trough concentration at the end of the dosing interval; AUC_{0–12} = area under the plasma concentration-time curve; C_{max} = maximum concentration; T_{max} = time to maximum concentration; T_{1/2} = half-life.