Inadequate Lopinavir Concentrations With Modified 8-hourly Lopinavir/Ritonavir 4:1 Dosing During Rifampicin-based Tuberculosis Treatment in Children Living With HIV

Background: Lopinavir/ritonavir plasma concentrations are profoundly reduced when co-administered with rifampicin. Super-boosting of lopinavir/ritonavir is limited by nonavailability of single-entity ritonavir, while double-dosing of co-formulated lopinavir/ritonavir given twice-daily produces suboptimal lopinavir concentrations in young children. We evaluated whether increased daily dosing with modified 8-hourly lopinavir/ritonavir 4:1 would maintain therapeutic plasma concentrations of lopinavir in children living with HIV receiving rifampicin-based antituberculosis treatment.

Methods: Children with HIV/tuberculosis coinfection weighing 3.0 to 19.9 kg, on rifampicin-based antituberculosis treatment were commenced or switched to 8-hourly liquid lopinavir/ritonavir 4:1 with increased daily dosing using weight-band dosing approach. A standard twice-daily dosing of lopinavir/ritonavir was resumed 2 weeks after completing antituberculosis treatment. Plasma sampling was conducted during and 4 weeks after completing antituberculosis treatment.

Results: Of 20 children enrolled; 15, 1–7 years old, had pharmacokinetic sampling available for analysis. Lopinavir concentrations (median [range]) on 8-hourly lopinavir/ritonavir co-administered with rifampicin (n = 15; area under the curve 0–24 55.32 mg/h/L [0.30–398.7 mg/h/L]; Cmax 3.04 mg/L [0.03–18.6 mg/L]; C8hr 0.90 mg/L [0.01–13.7 mg/L]) were lower than on standard dosing without rifampicin (n = 12; area under the curve 121.63 mg/h/L [2.56–487.3 mg/h/L]; Cmax 9.45 mg/L [0.39–26.4 mg/L]; C8hr 0.03 mg/L [0.01–17.7 mg/L]). During and after rifampicin cotreatment, only 7 of 15 (44.7%) and 8 of 12 (66.7%) children, respectively, achieved targeted pre-dose lopinavir concentrations ≥1 mg/L.

Conclusions: Modified 8-hourly dosing of lopinavir/ritonavir failed to achieve adequate lopinavir concentrations with concurrent antituberculosis treatment. The subtherapeutic lopinavir exposures on standard dosing after antituberculosis treatment are of concern and requires further evaluation.

Key Words: HIV, lopinavir/ritonavir, pharmacokinetics, rifampicin, tuberculosis

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Model-based simulations predicted that increasing the daily dose of the commercially available LPV/r 4:1 liquid formulation, together with reduction of the dosing interval from 12- to 8-hourly could maintain recommended lopinavir concentrations of 1 mg/L or above in 95% of children. Rabie et al demonstrated that this approach achieved the target pre-dose concentrations of lopinavir (≥1 mg/L) in two-thirds of children with no serious adverse events, but fell short of the model-predicted 95% target. We aimed to assess whether an increased daily dose of LPV/r, administered 8-hourly, would achieve adequate lopinavir blood concentrations in HIV-infected children receiving rifampicin-based TB treatment.

METHODS

This was a prospective pharmacokinetic study nested in the Shorter Treatment for Minimal Tuberculosis in Children (SHINE) trial (ISRCTN63579542). Children living with TB/HIV, weighing 3.0 to <20 kg, on LPV/r-based ART and rifampicin-containing TB treatment were enrolled in Lusaka, Zambia. Children were excluded if they had preexisting hepatic disease or liver enzymes levels more than twice the upper limit of normal.

Children receiving LPV/r (4:1), administered as Kaletra oral liquid (AbbVie Inc., North Chicago, IL), were switched from 12-hourly to 8-hourly dosing strategy. Eight-hourly LPV/r was dosed according to weight bands with children receiving 20–22 mg/kg in the highest 18–19.9 kg weight-band and 31–40 mg/kg in the lowest 3–3.9 kg weight-band. The doses of LPV/r 4.1 were adjusted 11%–33% upwards compared with the dosages used by Rabie et al, in increments pragmatic to administrator using the liquid formulation (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/F173). At the time of the study, LPV/r was recommended for children <5 years old initiating ART in Zambia as preferred first-line ART but super-boosting with additional ritonavir for cotreatment with rifampicin was not practiced due to non-availability of single formulated ritonavir. LPV/r was administered in combination with 2 NRTIs (abacavir or zidovudine with lamivudine). Children received rifampicin 15 mg/kg daily co-formulated with isoniazid 10 mg/kg administered as dispersible fixed-dose combination tablets of rifampicin and isoniazid 75/50 mg using World Health Organization (WHO) recommended weight bands for the continuation phase of TB treatment. Dosing was switched to WHO-recommended 12-hourly LPV/r 2 weeks after stopping rifampicin-based TB treatment.

Two intensive pharmacokinetic sampling days were conducted to assess lopinavir plasma concentrations: on 8-hourly LPV/r dosing; and 2 weeks after returning to 12-hourly dosing. The children were fasted before pharmacokinetic sampling until at least 1–2 hours after the dosing depending on the age of the patient. Samples were obtained before the LPV/r dose and at 1, 2, 4, 6, and 8 hours post-dose on 8-hourly dosing, with an additional 12-hour post-dose sample on 12-hourly dosing. Plasma concentrations of lopinavir and ritonavir were determined using validated liquid chromatography-mass spectrometry at the University of Cape Town pharmacology laboratory using methods previously described. The lower limits of quantification of the lopinavir and ritonavir assays were 0.0195 and 0.00488 mg/L, respectively.

A therapeutic efficacy target of pre-dose lopinavir concentration of ≥1.0 mg/L was used as the primary pharmacokinetic endpoint. Proportions of children with Cmin or Cmax below this target during rifampicin cotreatment or post-rifampicin treatment, respectively, were assessed. Association between the primary endpoint with patient parameters was determined using t test and χ2 tests. Geometric mean ratio (GMR), with 90% confidence interval (CI), for the area under the curve (AUC) during rifampicin cotreatment or post-rifampicin treatment, respectively, were compared during the 2 time periods for children with paired observations. AUC24 was derived by multiplying AUC8 and AUC12 by 3 and 2, respectively. Noncompartmental analysis was used to derive the pharmacokinetic parameters using Stata version 17.0 (StataCorp, College Station, TX).

RESULTS

Of 20 participants enrolled, 16 underwent intensive sampling and provided 15 (174 sampling points on rifampicin) and 12 (84 sampling points without rifampicin) evaluable pharmacokinetics profiles for analysis. The pharmacokinetic profile from 1 child with undetectable lopinavir concentrations during rifampicin treatment was excluded from the analysis. Four participants missed the 2nd sampling day (off rifampicin), 3 due to COVID-19 restrictions and 1 due to relocation. The median (range) age at enrollment was 3 years (1–7 years) with median (interquartile range [IQR]) weight-for-age Z scores (WAZ) of –1.6 (–2.3 to –0.9). Five were ART-naive while the rest were on LPV/r-based ART at enrollment with a median (IQR) duration of ART of 4.2 months (2.7–17.4 months). All children received abacavir/lamivudine as the NRTI backbone. The median (IQR) lopinavir dosages were 69.8 mg/kg/d (68.1–75.0 mg/kg/d) versus 26.6 mg/kg/d (24.1–27.3 mg/kg/d), during 8-hourly and 12-hourly dosing, respectively. The median rifampicin (IQR) dose was 15.2 mg/kg/d (13.4–17.4 mg/kg/d) (Table 1).

The median (IQR) lopinavir concentrations (AUC24, 55.32 mg·h/L [5.61–222.18 mg·h/L]; Cmax, 3.04 mg/L)

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<th>TABLE 1. Patient Characteristics and Pharmacokinetic Measures During 8-hourly and 12-hourly Lopinavir/ Ritonavir Dosing</th>
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<td><strong>Cmin ≥1mg/L, n (%)</strong></td>
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*GMR for paired data in the 1st and 2nd pharmacokinetic sampling session.
†AUC8 was derived by multiplying 3 × AUC during rifampicin cotreatment and 2 × AUC post-rifampicin cotreatment.
PK indicates pharmacokinetics; WHZ, weight-for-height Z score.

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Modified LPV/r Dosing With Rifampicin

[0.62–12.70 mg/L; C∞hr 0.90 mg/L [0.04–4.39 mg/L]) during treatment with rifampicin were lower than after rifampicin treatment (AUC24 121.63 mg/h/L [35.85–353.81 mg/h/L]; Cmax 9.45 mg/L [3.03–17.70 mg/L]; C12hr 3.03 mg/L [0.54–9.39 mg/L]). Only 7 of 15 (44.7%) achieved the recommended lopinavir pre-dose concentration of ≥1 mg/L during rifampicin treatment compared with 8 of 12 (66.7%) without rifampicin. This result was despite higher milligram per kilogram lopinavir dose (median 23.3 mg/kg) in 8-hourly doses during treatment with rifampicin compared with the 12-hourly doses (median 13.3 mg/kg) without rifampicin (Fig. 1 and Table 1). The pre-dose

FIGURE 1. Lopinavir pharmacokinetic profiles during and after cotreatment with rifampicin. Pharmacokinetic profiles of lopinavir during cotreatment with rifampicin (A) and post-tuberculosis treatment (B). Each line in (A) and (B) represents the pharmacokinetic profile for individual participants sampled in the first and second intensive pharmacokinetic sampling session. The dotted red horizontal line represents the reference Lopinavir pre-dose target concentration of 1 mg/L.
lопинавир концентрация была на 65% ниже при лечении рифампицином, чем при отсутствии рифампицина (Cₘₚ, GMR 0.35, 90% CI: 0.30–0.38). Сильно низкие концентрации лопинавира были обнаружены у 24 часов после проведения терапии рифампицином (AUC, GMR 0.35, 90% CI: 0.21–0.61; Cₘₚ, GMR 0.39, 90% CI: 0.24–0.64) (Таблица 1). Наблюдалось ассоциация между диапазоном P = 0.74 и WAZ (P = 0.13) с пред-дозой лопинавир.

Виральный нагрузка (VL) измерения были проведены как по национальным руководствам и были доступны для 6 участников к моменту обследования; 4 из которых имели VL >1000 copies/mL. Результаты после TB лечение были доступны для 9 участников (средний ART продолжительность 9.6 месяцев); 2 участника имели пост-ТБ лечение VL >1000 copies/mL, в то время как 4 из 3 участников имели VL между 50–1000 copies/mL и <50 copies/mL, соответственно. В целом, наблюдалась 4-логарифмичная скала в VL между обследованием и пост-терапией.

Мы получили ретроспективные данные о хранении лекарств и соблюдении режима у 10 из 10 участников. Два участника были госпитализированы на 2 отдельных случая пневмонии и острого гастроэнтерита, в то время как остальные участники не требовали отмены лечения. Один участник был госпитализирован на 2 отдельных случая, в то время как другие участники не имели острого гастроэнтерита или пневмонии.

В нашем исследовании, модифицированный 8-часовой подход с увеличенным интервалом между дозами лопинавир/ритонавира 4:1 не позволил достичь необходимых концентраций лопинавира у детей, которые получали рифампицин. Лопинавир концентрации были низкими как при 8-часовом режиме, так и при стандартном 12-часовом режиме после достижения рифампициновой терапии. Уменьшение концентраций не достигало рекомендуемых концентраций 1 мг/л для лопинавира плазмы дозы транзитом, в то время как стандартная доза лопинавир/ритонавир не обеспечивала целевой лопинавир концентрации. Мы использовали обратную связь в клинике только в день сбора образцов, 3 ухода за пациентом и лечение были проведены за 3 дня до дня проведения образцов.

Мы исследовали ретроспективные данные о хранении лекарств и соблюдении режима у 10 из 10 участников. Два участника были госпитализированы на 2 отдельных случаев для наблюдения за Калетру сиропом в холодильнике, 6 из 10 вернули препараты в холодильник, а остальные участники предоставили информацию о хранении лекарств. В целом, 3 участника сообщили об угрозе хранения лекарств.

При анализе данных, у 3 участников наблюдался небольшой рост событий, включая 2 случая, которые были отмечены у одного из уходов за пациентом. Один участник был госпитализирован на 2 отдельных случая для наблюдения за Калетру сиропом в холодильнике, 6 из 10 вернули препараты в холодильник, а остальные участники предоставили информацию о хранении лекарств.

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strategies are required for children with HIV/TB. This study highlights the importance of conducting dose-optimization studies in different pediatric populations to confirm model-predicted dosing for one of the alternative cotreatment strategies. This study and other pediatric pharmacokinetic studies demonstrated that increasing the daily dose and frequency to 8-hourly of standard LPV/r liquid formulation resulted in suboptimal therapeutic lopinavir levels. Although the interpretation of our findings is complicated by lower-than-expected lopinavir exposures without rifampicin, this study supports the findings of Rabie et al., which used lower model-predicted 8-hourly doses, and in which the approach failed to counter the inducing effect of rifampicin. The 8-hourly dosing approach cannot therefore be relied upon as an alternative option for TB cotreatment. This supports the rapid roll out of doctegavir-based treatment in TB endemic countries where the challenges of HIV/TB cotreatment persist, as well as the roll out of child-friendly ritonavir formulations for lopinavir super-boosting for children unable to take doctegavir. The subtherapeutic concentrations of lopinavir with the use of LPV/r liquid without rifampicin co-administration requires further evaluation and supports the use of more heat stable formulations such as granules or tablets especially in environments where storage conditions may not be assured.

APPENDIX


ACKNOWLEDGMENTS

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