Lopinavir/ritonavir significantly influences pharmacokinetic exposure of artemether/lumefantrine in HIV-infected Ugandan adults

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Background: Treatment of HIV/malaria-coinfected patients with antiretroviral therapy (ART) and artemisinin-based combination therapy has potential for drug interactions. We investigated the pharmacokinetics of artemether, dihydroartemisinin and lumefantrine after administration of a single dose of 80/480 mg of artemether/lumefantrine to HIV-infected adults, taken with and without lopinavir/ritonavir.

Methods: A two-arm parallel study of 13 HIV-infected ART-naive adults and 16 HIV-infected adults stable on 400/100 mg of lopinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors (ClinicalTrials.gov, NCT 00619944). Each participant received a single dose of 80/480 mg of artemether/lumefantrine under continuous cardiac function monitoring. Plasma concentrations of artemether, dihydroartemisinin and lumefantrine were measured.

Results: Co-administration of artemether/lumefantrine with lopinavir/ritonavir significantly reduced artemether maximum concentration (C_{max}) and area under the concentration–time curve (AUC) [median (range): 112 (20–362) versus 56 (17–236) ng/mL, $P=0.03$; and 264 (92–1129) versus 151 (38–606) ng·h/mL, $P<0.01$]. Dihydroartemisinin C_{max} and AUC were not affected [66 (10–111) versus 73 (31–224) ng/mL, $P=0.55$; and 213 (68–343) versus 175 (118–262) ng·h/mL $P=0.27$]. Lumefantrine C_{max} and AUC increased during co-administration [2532 (1071–5957) versus 7097 (2396–9462) ng/mL, $P<0.01$; and 41119 (12850–125200) versus 199678 (71205–251015) ng·h/mL, $P<0.01$].

Conclusions: Co-administration of artemether/lumefantrine with lopinavir/ritonavir significantly increases lumefantrine exposure, but decreases artemether exposure. Population pharmacokinetic and pharmacodynamic trials will be highly valuable in evaluating the clinical significance of this interaction and determining whether dosage modifications are indicated.

Keywords: antiretrovirals, antimalarials, drug interactions

Introduction

Malaria and HIV are two infectious diseases causing significant morbidity and mortality worldwide. The two diseases have overlapping geographical distribution in sub-Saharan Africa, where over 90% of the world malaria burden and 67% of the global HIV burden occur.[1,2] Significant interactions occur between the two diseases, with HIV increasing the risks for malaria frequency and severity.[3,4] Infection with malaria stimulates immune mechanisms that activate HIV replication, causing a transient increase in HIV viral load.[5,6]

Major effort has been made to ensure universal access to antiretroviral therapy (ART), with significant improvement in quality of life and survival of people living with HIV. In 2009,

1.2 million people were initiated on ART, a 30% increase in ART coverage in one year.[7] Successful treatment of infectious diseases such as HIV and malaria requires adequate drug concentrations at the target site to produce maximal efficacy with minimal toxicity. Drug pharmacokinetics might be influenced by drug–drug interactions. Antiretroviral drugs, specifically the non-nucleoside reverse transcriptase inhibitors and protease inhibitors, are potent inducers and/or inhibitors of cytochrome (CYP) enzymes and transporter proteins, with potential for drug–drug interactions when co-administered with other drugs.[8,9]

The WHO recommends artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria.[2] The combination of artemether and lumefantrine offers excellent efficacy against susceptible and multidrug-resistant *Plasmodium falciparum*. Both artemether and lumefantrine are metabolized predominantly by CYP3A4.[10] Artemether is metabolized to dihydroartemisinin, predominantly by CYP3A4/5 and to a lesser extent by CYP2B6, CYP2C9, CYP2C19 and possibly CYP2A6.[8,10–12] Dihydroartemisinin is rapidly converted into inactive metabolites primarily by glucuronidation via uridine diphosphoglucuronyltransferases (UGTs) UGT1A1, UGT1A8/9 and UGT2B7.[10,12–14] Both artemether and dihydroartemisinin possess potent antimalarial properties, causing a rapid reduction in asexual parasite biomass, with prompt resolution of symptoms.[15,16]

Lumefantrine is slowly eliminated, mainly metabolized by CYP3A4 to desbutyl-lumefantrine.[10–12] Lumefantrine eradicates residual malaria parasites thereby preventing recrudescence.[10,13,14] Total exposure to lumefantrine predicts parasite eradication and is the principal pharmacokinetic correlate of artemether/lumefantrine treatment.[16]

Lopinavir and ritonavir are inhibitors of CYP3A4, so co-administration with artemether/lumefantrine may result in increased artemether and lumefantrine plasma concentrations. Elevated lumefantrine plasma concentrations are of particular concern because of the structural similarity to halofantrine, a drug associated with cardiac arrythmias and sudden death.[17–19] In a previous study, co-administration of lopinavir/ritonavir with artemether/lumefantrine to healthy volunteers resulted in significantly increased lumefantrine exposure, decreased dihydroartemisinin exposure and a trend towards decreased artemether exposure.[20]

The aim of the present study was to investigate the pharmacokinetics of artemether, dihydroartemisinin and lumefantrine after administration of a single dose of 80/480 mg of artemether/lumefantrine to HIV-infected adults, taken with and without lopinavir/ritonavir-based ART. To avoid unknown adverse effects, we administered a single dose of artemether/lumefantrine to HIV-infected patients without malaria and vigilantly monitored their cardiac function.

Methods

Study site

The study was conducted between January 2008 and June 2009 at the Infectious Diseases Institute (IDI) and the Uganda Heart Institute, Mulago Hospital, Kampala, Uganda.

Study design and population

This was a two-arm parallel study to assess the pharmacokinetics of a single dose of artemether/lumefantrine co-administered with and without lopinavir/ritonavir-based ART to HIV-infected patients without malaria. Patients were eligible to participate if they were older than 18 years, with no evidence of systemic illness and no indication for medications with known potential for drug interactions with the study drugs. Patients with abnormal cardiac, liver or renal function, positive blood smear for malaria, pregnant mothers and those who reported use of any herbal medication were excluded.

Ethical considerations

The study was approved by the Uganda National HIV/AIDS Research Committee (ARC 056) and the Uganda National Council of Science and Technology (HS 195), and was registered with ClinicalTrials.gov (NCT 00619944). Study procedures were explained to participants in their local languages. Each participant received an information leaflet to take home. All participants provided written informed consent prior to study entry. Study procedures were conducted in accordance with the principles of Good Clinical Practice.

Study procedures

Patients were screened and enrolled consecutively from the cohort of patients attending the IDI. The artemether/lumefantrine plus lopinavir/ritonavir arm consisted of HIV-positive patients stable on 400/100 mg of lopinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors (NRTIs) taken twice daily for at least 1 month. The artemether/lumefantrine arm consisted of HIV-positive ART-naive patients who had not started ART and were not yet eligible for ART according to national guidelines. Patients in both arms took co-trimoxazole daily for prophylaxis against opportunistic infections. Adherence to study drugs was assessed using self-report and pill count at each clinical visit. On the evening prior to the study day, participants were reminded of their study-day appointment and were given detailed instructions to eat food; those in the lopinavir/ritonavir arm were reminded to administer their ART by 8.00 pm, and arrive at the hospital by 7.00 am in a fasting state.

On the morning of the study day, patients were admitted to the Heart Institute. Blood smears for malaria parasites were performed, and patients found to have positive smears were given a standard six-dose course of artemether/lumefantrine and excluded from further study. A 12-lead electrocardiograph (ECG) monitor was attached for continuous cardiac function monitoring. An indwelling intravenous catheter was inserted following aseptic techniques, and blood samples were drawn for the determination of pre-dose concentrations of artemether, dihydroartemisinin and lumefantrine. A standardized breakfast with added fat to cater for the fat requirement for artemether/lumefantrine absorption was administered.[21] The intake of breakfast and study drugs was directly observed by study staff.

All patients took a single dose of four tablets, equivalent to 80/480 mg of artemether/lumefantrine (Coartem®, Novartis Pharma AG, Basel, Switzerland; Batch number: F0660) with water immediately after breakfast. Patients in the lopinavir/ritonavir arm took 400/100 mg of lopinavir/ritonavir (Aluvia®, Abbott Laboratories, USA) plus two NRTIs with their study artemether/lumefantrine dose. The NRTI combination consisted of zidovudine plus didanosine, or tenofovir plus emtricitabine.

Sampling was performed at 1, 2, 4, 6, 8, 12, 24, 48 and 72 h post-artemether/lumefantrine dosing. An aliquot of 4 mL of blood was collected per sampling time in lithium–heparin tubes. Samples were centrifuged immediately for 10 min; plasma was separated and stored immediately at −70°C until shipment on dry ice to the Clinical Pharmacology Laboratory, Mahidol-Oxford Tropical Medicine Research Unit,

Mahidol University, Bangkok, Thailand for measurement of artemether, dihydroartemisinin and lumefantrine plasma concentrations.

Safety assessment

Medical history, physical examination, routine clinical laboratory tests, ECG and urine screens for pregnancy were performed at screening. On the study day, medical history, physical examination and blood smears for malaria parasites were performed. Standard 12-lead ECGs were recorded at screening, immediately prior to dosing, then continuously for 12 h post-dose of artemether/lumefantrine and once daily for 3 days thereafter. Participants were monitored for adverse events until 2 weeks post-sampling; the onset, duration, severity and relationship to the trial drugs (if any) were noted.

Artemether, dihydroartemisinin and lumefantrine plasma concentration measurement

Artemether and dihydroartemisinin concentrations were measured using solid-phase extraction and liquid chromatography/mass spectrometry.[22] Total-assay coefficients of variation for dihydroartemisinin and artemether during analysis were less than 5% at all quality control levels. The lower limit of quantification was 1.4 ng/mL and the limit of detection was 0.5 ng/mL for both drugs.[22]

Lumefantrine concentrations were determined using a solid-phase extraction/liquid chromatographic assay with ultraviolet detection.[23] The coefficient of variation was less than 6% at all quality control levels. The lower limit of quantification was 25 ng/mL and the limit of detection was 15 ng/mL.[23]

Analytical and pharmacokinetic methods

Non-compartmental analysis was performed using WinNonlin Professional[TM] software, version 5.2 (Pharsight Corp., Mountain View, CA, USA). Pharmacokinetic parameters included the observed maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration–time curve from zero to the last observation (AUC_{0-last}), area under the plasma concentration-time curve from zero extrapolated to infinity ($AUC_{0-\infty}$), elimination clearance (CL/F), apparent volume of distribution (V/F), elimination half-life ($t_{1/2}$) and absorption lag time (T_{lag}). The trapezoidal rule (linear-up/log-down) was used to estimate AUC. All parameters were calculated using actual blood sampling times. Drug concentrations below the lower limit of quantification of the bioanalytical assays were treated as missing data. The median values and ranges of the pharmacokinetic parameters were recorded for the two groups.

Statistical analysis

Data were analysed using STATA® version 10.0 (StataCorp, College Station, TX, USA). Baseline characteristics were summarized as mean with 95% CI and compared using the independent t-test. The Wilcoxon rank-sum test was used to compare pharmacokinetic parameters between the two groups. A P value of <0.05 was considered statistically significant.

Results

A total of 36 participants were enrolled, of whom 29 completed the 72 h sampling. Of the seven participants who did not complete sampling, two dropped out before sampling started, one participant had only the first three samples drawn due to difficulty with cannulation and four patients had positive blood smears for malaria on the sampling visit; the latter were given the standard six-dose regimen of artemether/lumefantrine and excluded from further study.

Analyses were performed on data from the 29 participants who completed sampling: 16 [9 (56%) female] in the artemether/lumefantrine plus lopinavir/ritonavir arm, and 13 [9 (69%) female] in the artemether/lumefantrine arm. All participants taking lopinavir/ritonavir-based ART had viral load below the level of detection (400 copies/mL). Mean (95% CI) of the log of viral load was 4.5 (4.0–5.0) copies/mL among the ART-naive patients. Participants in the two study arms were comparable for all other baseline characteristics measured except haemoglobin, which was significantly higher among patients taking lopinavir/ritonavir-based ART (Table 1). All participants tolerated study drugs very well, with no adverse events reported. ECG parameters for patients in both study arms remained well within normal limits throughout the 72 h follow-up period. These data have been published elsewhere.[24]

Effect of lopinavir/ritonavir on artemether and dihydroartemisinin pharmacokinetics

Co-administration of artemether/lumefantrine with lopinavir/ritonavir significantly increased artemether CL/F and V/F, by 67% (P<0.01) and 39% (P=0.02), respectively. Artemether C_{max} and AUC_{0-last} were significantly reduced, by 50% (P=0.03) and 43% (P<0.01), respectively (Table 2 and Figure 1a). Dihydroartemisinin CL/F and V/F were not influenced by lopinavir/

Table 1. Baseline characteristics of study participants

Variable	Mean (95% CI)		P value
	artemether/ lumefantrine arm	artemether/lumefantrine plus lopinavir/ritonavir arm	
Age (years)	34.5 (29.9–39.0)	37.6 (34.3–40.9)	0.2
Body weight (kg)	63.8 (58.1–69.5)	64.0 (57.6–70.5)	0.9
Height (cm)	160.1 (155.2–165.0)	165.8 (161.5–170.0)	0.06
Body mass index (kg/m^2)	25.1 (22.2–28.0)	23.4 (21.0–25.8)	0.3
Haemoglobin (mg/dL)	12.6 (11.4–13.8)	14.3 (13.8–14.9)	0.004[a]
QTc (ms)	411.5 (402.3–420.6)	416.8 (406.0–427.5)	0.4

[a]Statistically significant.

Table 2. Comparison of pharmacokinetic parameters of artemether, dihydroartemisinin and lumefantrine

Parameter	Artemether/lumefantrine ($N=13$), median (range)	Artemether/lumefantrine plus lopinavir/ritonavir ($N=16$), median (range)	P value
Artemether			
C_{max} (ng/mL)	112 (20–362)	56 (17–236)	0.03
T_{max} (h)	1 (1–4)	2 (1–4)	0.38
CL/F (L/h)	295 (69–817)	492 (129–1805)	<0.01
V/F (L)	1072 (593–2651)	1487 (762–3485)	0.02
$t_{1/2}$ (h)	2 (1–5)	1 (1–6)	0.04
$AUC_{0\text{-last}}$ (ng·h/mL)	264 (92–1129)	151 (38–606)	<0.01
$AUC_{0\text{-}\infty}$ (ng·h/mL)	271 (97–1150)	162 (44–618)	<0.01
Dihydroartemisinin			
C_{max} (ng/mL)	66 (10–111)	73 (31–224)	0.55
T_{max} (h)	2 (1–4)	2 (1–4)	0.89
CL/F (L/h)	350 (210–942)	424 (280–626)	0.23
V/F (L)	922 (498–4779)	876 (734–1315)	1
$t_{1/2}$ (h)	1 (1–3)	1 (1–2)	0.06
$AUC_{0\text{-last}}$ (ng·h/mL)	213 (68–343)	175 (118–262)	0.27
$AUC_{0\text{-}\infty}$ (ng·h/mL)	217 (81–363)	180 (121–272)	0.23
Lumefantrine			
T_{lag} (h)	1 (0–4)	1 (0–1)	0.16
C_{max} (ng/mL)	2532 (1071–5957)	7097 (2396–9462)	<0.01
T_{max} (h)	8 (3–12)	8 (4–12)	0.26
CL/F (L/h)	10 (3–32)	1 (1–5)	<0.01
V/F (L)	179 (53–860)	86 (59–219)	0.01
$t_{1/2}$ (h)	23 (6–51)	31 (24–43)	<0.01
$AUC_{0\text{-last}}$ (ng·h/mL)	41119 (12850–125200)	199678 (71205–251015)	<0.01
$AUC_{0\text{-}\infty}$ (ng·h/mL)	46925 (14559–136297)	267386 (84845–344468)	<0.01

ritonavir co-administration. Similarly dihydroartemisinin C_{max} and $AUC_{0\text{-last}}$ were unaffected (Table 2 and Figure 1b).

### Effect of lopinavir/ritonavir on lumefantrine pharmacokinetics

Co-administration of artemether/lumefantrine with lopinavir/ritonavir significantly reduced lumefantrine CL/F and V/F, by 90% ($P<0.01$) and 52% ($P=0.01$), respectively. Lumefantrine C_{max} increased significantly by 180% ($P<0.01$) and $AUC_{0\text{-last}}$ by 386% ($P<0.01$) (Table 2 and Figure 1c).

Discussion

We investigated the pharmacokinetics of artemether, dihydroartemisinin and lumefantrine after administration of a single dose of 80/480 mg of artemether/lumefantrine to HIV-infected adults, taken with and without lopinavir/ritonavir-based ART. Co-administration of artemether/lumefantrine with lopinavir/ritonavir significantly increased artemether clearance with a consequently significant reduction in artemether exposure. Dihydroartemisinin pharmacokinetic parameters were not affected by lopinavir/ritonavir. Lumefantrine clearance significantly decreased with a consequently significant increase in exposure.

Our data for the direction of the interaction between lopinavir/ritonavir and artemether/lumefantrine show a similar trend to data from a previous study by German *et al*.;[20] however, differences in the magnitude of the interaction as well as the effect on dihydroartemisinin were evident between the two studies. The previous study demonstrated a trend towards decreased artemether exposure, significant reduction in dihydroartemisinin exposure and significant increase in lumefantrine exposure following standard six-dose artemether/lumefantrine administration with lopinavir/ritonavir to 13 healthy HIV-seronegative adults.[20] The differences in the results from the two studies possibly arise from differences in the study designs and population. German *et al*.[20] conducted a sequential cross-over study in which artemether/lumefantrine parameters were compared within the same individuals with and without lopinavir/ritonavir, while we employed a parallel study design with comparison of parameters from different individuals with and without lopinavir/ritonavir. The parallel study design was adequate for the objectives of our study, but has a limitation due to the high inter-individual variability of artemether and dihydroartemisinin. Comparison of pharmacokinetic exposures in the same individuals using the sequential design was not feasible given that lopinavir/ritonavir is used for second-line HIV treatment in our study setting.

In addition, our population was composed of HIV-infected adults of African origin, unlike the HIV-uninfected healthy

(a)

(b)

(c)
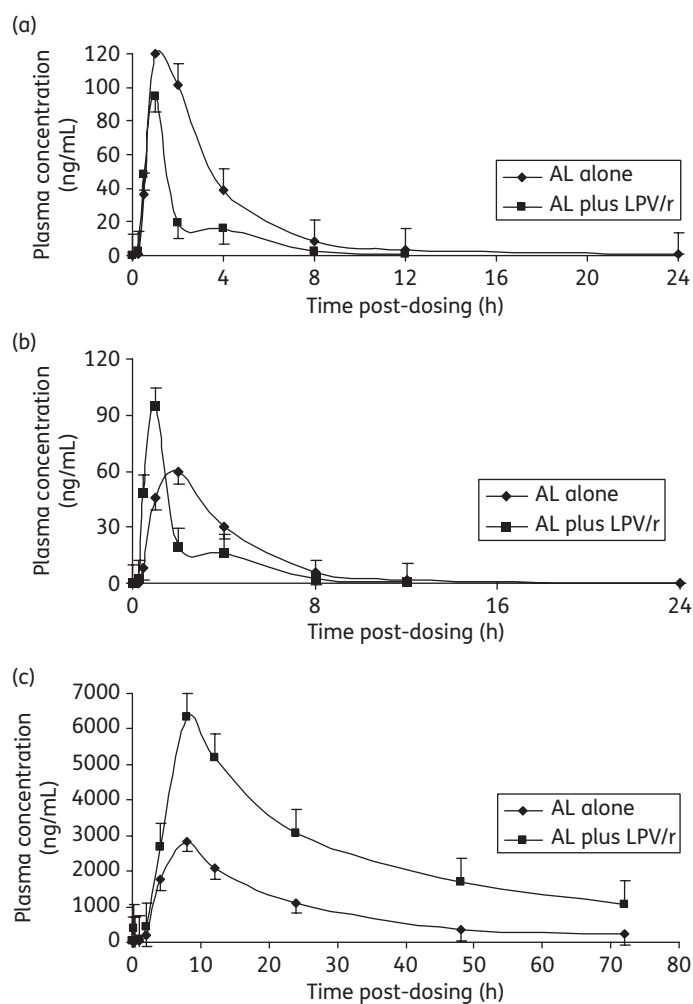
Figure 1. Mean ($\pm$SEM) plasma concentration versus time of (a) artemether, (b) dihydroartemisinin and (c) lumefantrine for participants taking artemether/lumefantrine alone (AL alone) and artemether/lumefantrine in combination with lopinavir/ritonavir (AL plus LPV/r).

volunteers of primarily white origin in the study by German et al.[20] Genetic variation may cause inter-individual pharmacokinetic variability due to polymorphisms of genes encoding drug-metabolizing enzymes.[25–27] In addition, drug pharmacokinetics may differ in healthy volunteers compared with patients with disease.

Further differences in the magnitude of the effects of interaction between our data and the German et al.[20] data could have arisen from the six-dose compared with the single-dose regimen of artemether/lumefantrine. We administered a single dose of artemether/lumefantrine to avoid any unknown adverse effects of co-administration of artemether/lumefantrine with lopinavir/ritonavir in HIV-infected participants. German et al.[20] administered the standard six-dose artemether/lumefantrine regimen to healthy volunteers. Artemether undergoes auto-induction of its metabolism, and artemether/dihydroartemisinin ratios after 3 days of treatment with the standard dose are lower than those seen after a single dose.[28]

In both studies lumefantrine exposure was elevated during co-administration with lopinavir/ritonavir; however, despite the elevated lumefantrine exposure, participants tolerated the study drugs very well, with all reported adverse events consistent with what had previously been reported for artemether/lumefantrine and lopinavir/ritonavir. Our data did not demonstrate evidence of cardiac conduction abnormalities. However, caution and safety monitoring of HIV/malaria-coinfected patients receiving artemether/lumefantrine with lopinavir/ritonavir is advised. It will be important to determine if these effects are additive in the standard six-dose artemether/lumefantrine regimen in HIV/malaria-coinfected patients receiving lopinavir/ritonavir.

Ritonavir-boosted lopinavir influences the activity of several CYP enzymes and drug transporters such as the efflux transporter P-glycoprotein.[29] Both lopinavir and ritonavir inhibit intestinal and hepatic CYP3A4 and P-glycoprotein.[29,30] Inhibition of CYP3A4 or P-glycoprotein expression decreases biotransformation, resulting in an increase in bioavailability of co-administered substrates.[9,31–33] Previous data demonstrated increased artemether, dihydroartemisinin and lumefantrine exposure in the presence of the CYP3A4 inhibitors ketoconazole and grapefruit juice.[34,35] Inhibitions of CYP3A4 and P-glycoprotein are likely explanations for the increased lumefantrine exposure in our study.

The reduction in artemether exposure was unexpected, since CYP3A4 is suggested to be the predominant CYP enzyme in the metabolism of artemether.[10] Although artemether is predominantly metabolized via CYP3A4/5, other CYP enzymes (CYP2B6, CYP2C9, CYP2C19 and possibly CYP2A6) are involved.[10,13,14] Lopinavir/ritonavir was shown to induce CYP1A2, CYP2B6, CYP2C9, and CYP2C19.[30,36] The observed increased clearance and decreased artemether exposure is likely due to induction of these CYP enzymes by lopinavir/ritonavir.

Dihydroartemisinin is converted into inactive metabolites by UGT1A1, UGT1A8/9 and UGT2B7.[10,13,14] Induction and inhibition of UGTs by xenobiotics have been described previously, and lopinavir/ritonavir was shown to inhibit UGTs 1A1, 1A3, 1A4, 1A6, 1A9 and 2B7.[37–39] However, we found no statistical difference in the pharmacokinetic parameters of dihydroartemisinin after lopinavir/ritonavir co-administration compared with administration alone. The reason for this is unclear, but might be due to the small numbers and large inter-individual variability.

Artemether and dihydroartemisinin have very short half-lives and rapidly clear parasites from circulation.[11] Both are very potent antimalarial agents, although dihydroartemisinin is more potent.[16] Lumefantrine has a much longer half-life and mainly clears residual parasites, preventing recrudescence. Higher artemether and dihydroartemisinin exposure decreases parasite clearance time,[13] but the major determinant of radical cure is lumefantrine exposure.[40] Given that HIV/malaria-coinfected patients present with higher parasite counts,[3,41] which is an independent predictor of poor treatment response,[42] reduction in artemether exposure may predispose patients to develop severe malaria due to slower parasite clearance. The clinical relevance of the present findings should be interpreted with caution given that we administered a single artemether/lumefantrine dose while a six-dose artemether/lumefantrine regimen is administered for malaria treatment.

The reduction in artemether exposure by lopinavir/ritonavir after the single artemether/lumefantrine dose may be offset

by the increase in lumefantrine exposure. Previous data revealed that lumefantrine exposure is the key determinant for malaria cure,[43] therefore the increase in lumefantrine exposure during lopinavir/ritonavir co-administration may be beneficial for malaria cure. However, rapid clearance of artemether and reduced clearance of lumefantrine may create longer periods of exposure to lumefantrine monotherapy with the risk of development of resistance.

Conclusions

Co-administration of a single dose of artemether/lumefantrine with lopinavir/ritonavir significantly reduced artemether exposure, with a significant increase in lumefantrine exposure. Population pharmacokinetic and pharmacodynamic trials will be highly valuable in evaluating the clinical significance of this interaction and determining whether dosage modifications are indicated.

Transparency declarations

None to declare.

Author contributions

P. B.-K., M. L., S. K. and C. M. contributed to the design and conduct of the study. P. B.-K., M. L. and V. O.-K. participated in recruitment of patients and data collection. W. H. and N. L. performed the bioanalytical assays. P. B.-K., T. P. C. D., J. T., N. L. and P. J. d. V. analysed and interpreted the pharmacokinetic data. H. M.-K., E. K., N. P., P. J. d. V., D. B., S. K. and C. M., participated in training the study staff, and provided scientific support. P. B.-K. drafted the first version, and all authors reviewed and approved the manuscript for submission.

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