Lower artemether, dihydroartemisinin and lumefantrine concentrations during rifampicin-based tuberculosis treatment

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Objective: To investigate the pharmacokinetics of artemether, dihydroartemisinin and lumefantrine during rifampicin intake and after stopping rifampicin.

Study design: An open-label, two-phase, longitudinal drug interaction study with patients serving as their own controls.

Methods: We recruited HIV-1-seropositive Ugandan adults who were receiving rifampicin-based tuberculosis treatment and who did not have malaria. Pharmacokinetic sampling after six doses of artemether-lumefantrine was performed during rifampicin-based tuberculosis treatment (phase 1) and repeated at least 3 weeks after stopping rifampicin-based tuberculosis treatment (phase 2).

Results: Six and five patients completed phases 1 and 2, respectively. Median age and weight were 30 years and 64 kg. Artemether and dihydroartemisinin area under the concentration–time curve (AUC_{0-12h}) were significantly lower by 89% [geometric mean ratio (GMR) 90% confidence interval (CI) 0.11, 0.05–0.26] and 85% (0.15, 0.10–0.23), respectively, during rifampicin-based treatment when compared to AUC_{0-12h} after stopping rifampicin intake. Similarly, artemether and dihydroartemisinin C_{max} were 83% (0.17, 0.08–0.39) and 78% (0.22, 0.15–0.33) lower, respectively, during rifampicin treatment. For artemether, mean (±SD) C_{12} was 0.5(±1.0) and 5.9(±2.5) ng/ml in phases 1 and 2, respectively. Corresponding values for dihydroartemisinin (DHA) were 0.3(±0.4) and 4.7(±2.0) ng/ml, respectively. Day 8 lumefantrine concentration was significantly lower by 84% (GMR 90% CI 0.16, 0.09–0.27), and $AUC_{Day3\text{-}Day25}$ was significantly lower by 68% (GMR 90% CI 0.32, 0.21–0.49) during rifampicin-based treatment when compared to exposure values after stopping rifampicin.

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Received: 13 September 2012; revised: 5 November 2012; accepted: 15 November 2012.

DOI:10.1097/QAD.0b013e32835cae3b

Conclusion: Pharmacokinetic parameters for artemether-lumefantrine were markedly lower during rifampicin-based tuberculosis treatment. Artemether-lumefantrine should not be co-administered with rifampicin.

AIDS 2013, **27**:961–965

Keywords: artemether-lumefantrine combination, drug interactions, rifampicin

Introduction

Malaria and tuberculosis (TB) are co-endemic in many parts of the developing world. Although malaria transmission may occur throughout the duration of TB treatment, drug data between antimalarial drugs and anti-TB drugs are limited [1]. The WHO recommends artemisinin combination therapies (ACTs) for uncomplicated malaria caused by *Plasmodium falciparum*, whereas for TB treatment, the WHO recommends rifampicin-based therapy [2,3]. However, no data exist on drug interactions between ACTs and rifampicin-based TB treatment.

Artemether-lumefantrine is the most widely used ACT. Like other ACTs, it is composed of a short-acting artemisinin derivative that rapidly eliminates malaria parasites and a less potent but longer acting partner drug that eliminates residual parasites. Artemether is metabolized by cytochrome P450 3A4 (CYP3A4), CYP2B6, CYP2C9 and CYP2C19 to the pharmacologically active dihydroartemisinin (DHA), whereas formed DHA is subsequently inactivated by uridine diphosphate glucuronosyltranstransferase (UGT) 1A9 and 2B7 [4,5]. Artemether and DHA provide the most antimalarial activity of artemether-lumefantrine and higher exposure of these compounds are associated with an increased rate of clearance of malaria parasites [6]. Lumefantrine is metabolized to the pharmacologically active desbutyl-lumefantrine by CYP3A4. Lower concentrations of artemether and/or lumefantrine may increase the risk of malaria recrudescence [6].

An interaction with rifampicin is expected because rifampicin potently induces CYP3A4, CYP2B6, other CYP enzymes, UGTs and intestinal transporters such as P-glycoprotein (P-gp) [1,7]. Therefore, we investigated plasma pharmacokinetic parameters of artemether, DHA and lumefantrine among adult TB patients during rifampicin intake and after stopping rifampicin.

Methods

The study was an open-label, two-phase, longitudinal drug interaction study with patients serving as their own controls. The study was approved by the National AIDS Review Committee (ARC 059) and the protocol registered on www.ClinicalTrials.gov (NCT00620438). Consenting patients were recruited from the TB/HIV clinic of the Infectious Diseases Institute (IDI), Makerere University College of Health Sciences, Kampala. Patients were treated for TB in accordance with Uganda national treatment guidelines (an intensive phase involving daily treatment with rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months followed by a continuation phase with daily isoniazid and ethambutol for an additional 6 months). We included antiretroviral-naive TB/HIV-1 co-infected patients in the intensive phase of TB treatment. We excluded patients with malaria, severe anaemia (serum haemoglobin <8 g/dl), serum transaminases or creatinine greater than three times the upper limit of normal. Other exclusion criteria included pregnancy, QT prolongation or significant cardiac abnormalities, herbal medicine use or use of drugs which alter activity of CYP3A4 or P-glycoprotein. Patients on antiretroviral therapy (ART) were excluded because ART regimens include drugs that alter CYP3A4 activity.

Prior to each sampling phase, patients received six doses of artemether-lumefantrine (80 mg of artemether and 480 mg of lumefantrine in each dose) administered over 3 days (Beijing Novartis Pharma Ltd, Beijing, China). The first five doses were taken at home (at 0 h, 8 h and every 12 h thereafter) immediately after meals or with a glass of milk to ensure optimal absorption of lumefantrine. Dosing compliance was monitored by patient self-report. The sixth dose of artemether-lumefantrine was administered in the hospital after breakfast and under direct supervision of study staff. Blood sampling for artemether, DHA and lumefantrine determination in plasma was performed at least three weeks after patients had commenced rifampicin-based TB treatment (phase 1) and at least three weeks after stopping rifampicin intake (phase 2).

Anti-TB drugs were administered daily as fixed-dose combination tablets. In phase 1, patients received rifampicin, isoniazid, ethambutol and pyrazinamide. In phase 2, patients received ethambutol and isoniazid. Individual dosing times for anti-TB drugs were not changed. Throughout the study, all patients received daily

cotrimoxazole 960 mg once daily for opportunistic infection prophylaxis.

During each phase, 4 ml of venous blood was obtained at 0, 1, 2, 4, 8 and 12 h on Day 3 (i.e. after dose 6 of artemether-lumefantrine) for determination of artemether, DHA and lumefantrine concentrations. For lumefantrine, additional blood samples were collected on Days 4, 5, 8, 15, 20 and 25. Day 8 samples were obtained 7.3 days after first artemether-lumefantrine dose and used as a surrogate for standard Day 7 [8]. Blood samples were centrifuged to obtain plasma and stored at minus 70°C at the Makerere University – Johns Hopkins University Core Laboratory.

Plasma samples were shipped to the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand for quantification of artemether, dihydroartemisinin and lumefantrine. Artemether and dihydroartemisinin were quantified using liquid chromatography-tandem mass spectrometry [9]. The lower limit of quantification (LLOQ) for artemether and DHA was 1.4 ng/ml. For both analytes, accuracy of the assay ranged from 95.7 to 99.2%, whereas imprecision expressed as coefficients of variation was below 6.8% at all three quality control levels. Lumefantrine was determined by high performance liquid chromatography with ultraviolet detection [10]. The LLOQ for lumefantrine was 25 ng/ml. Accuracy of the assay ranged from 97.0–103.6%, whereas imprecision expressed as coefficient of variation (%) was below 5.0% at all three quality control levels.

Maximal plasma concentrations (C_{max}) and concentrations 12 h postdose (C_{12}) were directly obtained from the data. Elimination half-life ($t_{1/2\beta}$) and area under the concentration–time curve (AUC) were calculated by noncompartmental methods (WinNonlin Version 5.2; Pharsight, MountainView, California, USA) using actual sampling times and expressed as geometric means. Comparisons of phase 1 (with rifampicin) versus phase 2 (without rifampicin) parameters were performed using geometric mean ratio (GMR) and 90% confidence interval (CI). Paired pharmacokinetic parameters (phase 1 versus phase 2) were also compared using the Wilcoxon signed-rank test with P values 0.05 or less considered statistically significant. Lumefantrine concentrations were considered therapeutic if they were above 280 ng/ml 7.3 days after first artemether-lumefantrine dose (Day 8) [8].

Results

The study was terminated prematurely after enrolling seven patients in order to permit early commencement of ART in accordance with revised WHO guidelines for HIV/TB co-infected patients [11]. All seven patients had pulmonary TB. Pharmacokinetic data were available for six patients (five female) in phase 1 and five patients (four female) in phase 2. For these six patients, median (interquartile range) age and weight was 30 (26–41) years and 64 (57–68) kg. Median (range) CD4 cell count was 648 (464–1174) cells/μl. The seventh patient had no pharmacokinetic samples obtained at study discontinuation. One patient (patient #2) was discontinued during her phase 1 visit to permit treatment with fluconazole (an inhibitor of CYP3A4) for oropharyngeal candidiasis and was excluded from geometric mean comparisons.

Individual patient pharmacokinetic parameters for artemether, DHA and lumefantrine are shown in Table 1. Artemether and DHA AUC_{0-12h} were significantly lower by 89% (GMR 90% CI 0.11, 0.05–0.26; $P = 0.04$) and 85% (0.15, 0.10–0.23; $P = 0.04$), respectively, during rifampicin-based treatment when compared to AUC_{0-12h} after stopping rifampicin intake. Similarly,

Table 1. Individual patient pharmacokinetic parameters for artemether, DHA and lumefantrine during rifampicin intake (phase 1) and after stopping rifampicin intake (phase 2).

		Artemether		DHA		Lumefantrine	
Patient ID	Phase	C_{max} (ng/ml)	AUC_{0-12h} (ng.h/ml)	C_{max} (ng/ml)	AUC_{0-12h} (ng.h/ml)	Day 8 concentration (ng/ml)	$AUC_{Day3-Day25}$ (μg.h/ml)
#1	1	7	20	14	48	<LLOQ	49.6
	2	54	260	42	223	104	91.4
#2	1	24	32	36	63	NA	NA
#3	1	6	17	18	48	98	129
	2	83	314	107	405	1373	803
#4	1	71	188	54	132	85	107
	2	85	276	145	550	753	604
#5	1	6	19	11	29	126	311
	2	96	418	111	473	661	616
#6	1	3	8	8	31	122	113
	2	8	53	33	154	313	265

Note: Patient #2 attended only 12 h PK visit in phase 1 and had no phase 2 visit. AUC, area under the concentration time curve; C_{max}, maximum concentration; DHA, dihydroartemisinin; LLOQ, lower limit of quantification; NA, no samples available.

artemether and DHA C_{max} were 83% (0.17, 0.08–0.39; $P=0.04$) and 78% (0.22, 0.15–0.33; $P=0.04$) lower, respectively, during rifampicin treatment. For artemether, mean (±SD) C_{12} was 0.5(±1.0) and 5.9(±2.5) ng/ml in phases 1 and 2, respectively. Corresponding values for DHA were 0.3(±0.4) and 4.7(±2.0) ng/ml, respectively. For artemether, $t_{1/2\,\beta}$ (90% CI) was 2.1 (1.6–3.1) h with rifampicin and 3.7 (2.8–5.7) h after stopping rifampicin. For DHA, respective values for $t_{1/2\,\beta}$ were 1.5 (1.3–1.8) h and 2.4 (2.0–3.0) h.

Day 8 lumefantrine concentration was significantly lower by 84% (GMR 90% CI 0.16, 0.09–0.27; $P=0.04$) and $AUC_{Day3-Day25}$ was significantly lower by 68% (GMR 90% CI 0.32, 0.21–0.49; $P=0.04$) during rifampicin-based treatment when compared to exposure values after stopping rifampicin. Day 8 lumefantrine concentrations were below 280 ng/ml in all patients with rifampicin and 1/5 patients after stopping rifampicin intake. Lumefantrine $t_{1/2\beta}$ was 79.7 (46.7–272.9) h with rifampicin and 106.6 (70.4–219.7) h after stopping rifampicin intake.

Discussion

Systemic exposure to artemether, DHA and lumefantrine in TB patients given the six-dose regimen of artemether-lumefantrine was markedly lower during rifampicin-based TB treatment, whereas systemic exposure after stopping rifampicin intake was more consistent with previously reported data [5]. Although therapeutic thresholds for artemether and DHA have not been adequately defined, the markedly lower concentrations of these compounds during rifampicin treatment raise concerns that efficacy of these compounds could be diminished [8]. For logistic reasons, the study used the Day 8 time-point as a surrogate for Day 7 concentration. During rifampicin-based TB treatment, none of the studied patients attained lumefantrine concentrations higher than 280 ng/ml on Day 8. Below this threshold, approximately one half of treated malaria patients are at risk of experiencing recrudescence [8]. In this study, some rifampicin-treated patients already had concentrations below this value as early as the fifth day after starting treatment. Since higher lumefantrine exposure significantly increases the chance of cure [8], this interaction may lead to lower malaria cure rates in TB/malaria co-infected patients.

Theoretically, with CYP3A4 induction, increased conversion of artemether to DHA should lead to higher DHA concentrations. However, this study reports lower DHA exposure during rifampicin-based TB treatment. This is worrying because DHA contributes significantly to the antimalarial efficacy of artemether [4,5]. The reason for this finding is unknown but may relate either to rifampicin induction of intestinal efflux transporters like P-gp that limit absorption of artemether or induction of hepatic glucuronidation pathways which inactivate DHA.

In clinical practice, complex drug interactions may occur with artemether-lumefantrine. Under current guidelines, HIV/TB co-infected patients will require ART and rifampicin-based TB treatment simultaneously. If these patients develop malaria, antimalarial treatment will also be required. Significantly reduced artemether and DHA concentrations have recently been reported by the present study team among patients receiving efavirenz-based and nevirapine-based ART [12]. Based on the direction of these interactions, we postulate that systemic exposure to artemether, DHA and lumefantrine will be reduced in an interaction involving these three therapies.

We were unable to evaluate the pharmacodynamics of artemether-lumefantrine as the study patients did not have malaria. A recent clinical trial in South East Asia reported evidence of artemisinin resistance prompting global efforts to minimize the potential for artemisinin resistance [13,14]. The risk of resistance to artemether is considered low because of its short elimination half-life and because lumefantrine is also present during the first three days of treatment [8]. Relationships between parasite tolerance and drug exposure are yet to be defined; however, drug interactions which markedly distort the pharmacokinetics of artemether, DHA and lumefantrine may alter the risk profile for emergence of resistance. Emergence of artemisinin resistance has implications for malaria control efforts because no satisfactory alternatives to artemisinin derivatives exist with regard to efficacy and safety.

Based on data from the present study, the prescribing information of Coartem has been revised to state that concomitant use of artemether-lumefantrine with rifampicin is contraindicated [5]. In developing countries, satisfactory alternatives to ACTs are lacking. Oral quinine is available in developing countries but is contraindicated during rifampicin treatment [1]. Proguanil-atovaquone is not metabolized by CYP3A4 but it is more expensive than ACTs and rarely used in developing countries.

Drug–drug interaction data are not available for artemether-lumefantrine and other rifamycins. Rifampicin remains the preferred rifamycin in developing countries because of its low cost and availability as fixed-dose combination tablets that are widely used by national TB programmes. Rifabutin is a weaker enzyme inducer than rifampicin [1], but it is also more expensive and not widely available in developing countries. For rifampicin-treated patients in developing countries, malaria prevention should be emphasized and studies should be conducted to determine the optimal antimalarial treatment for these patients.

Acknowledgements

This paper is dedicated to the memory of Niklas Lindegårdh who was a co-investigator on this work.

We thank study patients and study team members (D. Ekusai, J. Nakku, H. Tibakabikoba and J. Magoola). Niklas Lindegårdh (deceased) contributed to the analysis and interpretation of the data.

Author contributions: C.M., M.R, P.B.-K. and M.L. contributed to the design of the study. M.L., P.B.-K., L.N. and J.M. participated in recruitment of patients and data collection. W.H. performed the bioanalytical assays. M.L. analysed the data. M.L., C.M., D.B., S.K. and G.L. interpreted the data. M.L. drafted the first version and all authors reviewed the manuscript and approved the final version of the manuscript.

Conflicts of interest

Funding: Health Research Board, Ireland (GHRA06/02).

Funding and other support: Health Research Board, Ireland (GHRA06/02). Additional logistics support was obtained from the Infectious Diseases Network for Treatment and Research in Africa; European and Developing Countries Clinical Trials Partnership (CT.2004.32011.003, TA.09.40200.020, TA.11.40200.047); Haughton Institute, Dublin and Gilead Foundation. WH is part of the Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme (077166/Z/05/Z). SK and DJB received support from a Wellcome Trust Programme grant for PK-PD modelling for HIV, TB and malaria (083851/Z/07).

Transparency declarations: G.L. is an employee of Novartis.

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