Pharmacokinetic and Pharmacodynamic Characteristics of a New Pediatric Formulation of Artemether-Lumefantrine in African Children with Uncomplicated Plasmodium falciparum Malaria

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The pharmacokinetic and pharmacodynamic properties of a new pediatric formulation of artemether-lumefantrine, dispersible tablet, were determined within the context of a multicenter, randomized, parallel-group study. In an exploratory approach, we compared a new pediatric formulation with the tablet formulation administered crushed in the treatment of African children with uncomplicated Plasmodium falciparum malaria. Patients were randomized to 3 different dosing groups (weights of 5 to <15 kg, 15 and <25 kg, and 25 to <35 kg). Treatment was administered twice daily over 3 days. Plasma concentrations of artemether and its active metabolite, dihydroartemisinin (DHA), were determined at 1 and 2 h after the first dose of dispersible (n = 91) and crushed (n = 93) tablets. A full pharmacokinetic profile of lumefantrine was reconstituted on the basis of 310 (dispersible tablet) and 315 (crushed tablet) plasma samples, collected at 6 different time points (1 sample per patient). Dispersible and crushed tablets showed similar artemether and DHA maximum concentrations in plasma (Cmax) for the different body weight groups, with overall means of 175 ± 168 and 190 ± 168 ng/ml, respectively, for artemether and 64.7 ± 58.1 and 63.7 ± 65.0 ng/ml, respectively, for DHA. For lumefantrine, the population Cmax were 6.3 µg/ml (dispersible tablet) and 7.7 µg/ml (crushed tablet), whereas the areas under the concentration-time curves from time zero to the time of the last quantifiable plasma concentration measured were 574 and 636 µg · h/ml, respectively. For both formulations, descriptive quintile analyses showed no apparent association between artemether/DHA Cmax and parasite clearance time or between the lumefantrine Cmax and the occurrence of adverse events or corrected QT interval changes. The results suggest that the dispersible tablet provides adequate systemic exposure to artemether, DHA, and lumefantrine in African children with uncomplicated P. falciparum malaria.

Artemisinin-based combination therapies (ACTs) are currently the best available treatments for uncomplicated Plasmodium falciparum malaria because of their fast action, reliable efficacy, good safety profile, and potential to lower the emergence and spread of drug resistance (2, 6, 18, 20). Artemether-lumefantrine (A-L; Coartem) was the first fixed-dose ACT prequalified by the World Health Organization (WHO) and has subsequently been adopted by many countries in sub-Saharan Africa as first-line treatment for uncomplicated P. falciparum malaria (26). The recommended 6-dose regimen of A-L, twice a day for 3 days, has been proven to be efficacious and safe in both infants and children weighing 5 to 35 kg and adults weighing ≥35 kg (11, 13, 15, 17).

In young children, A-L is usually administered as a crushed tablet (CT). In an effort to ease administration of A-L, a sweetened cherry-flavored A-L dispersible tablet (DT) formulation containing the same amounts of artemether and lumefantrine as the standard tablet was developed. Pharmacokinetic assessments were performed within a multicenter, investigator-blinded, randomized, noninferiority study comparing the efficacy and safety of DT and CT in African infants and children with uncomplicated P. falciparum malaria. The clinical efficacy and safety data have been presented elsewhere (1). This report focuses on the pharmacokinetics and the pharmacokinetic/pharmacodynamic (PK/PD) correlations assessed in large subgroups of patients. The specific objectives were to compare lumefantrine, artemether, and dihydroartemisinin (DHA) plasma levels between DT and CT and to assess potential relationships between these drug levels and safety and/or efficacy variables.

MATERIALS AND METHODS

Study design. Male or female infants and children with microscopically confirmed acute uncomplicated P. falciparum malaria were recruited from 8 health care facilities in Benin (n = 1 site), Kenya (n = 3), Mali (n = 1), Mozambique (n = 1), Tanzania (n = 1), and Tanzania/Zanzibar (n = 1). The multicenter...
study, including pharmacokinetic/pharmacodynamic assessments, was approved by the pertinent ethics committee of each participating center and is registered with ClinicalTrials.gov as NCT00386763. Before enrollment, written informed consent was obtained from the parents or legal guardians of the children (school-age children were additionally asked to give assent). The first patient was enrolled in August 2006, and the study was completed in March 2007. Criteria for inclusion and exclusion have been previously presented (1). Patients were randomized on a 1:1 basis to receive either A-L DT or CT (each containing 20 mg of artemether and 120 mg of lumefantrine) within 3 different dosing groups on the basis of body weight. Treatment was administered twice daily over 3 days. The children were hospitalized for the first 3 days to allow supervised dosing at exact times (at 0, 8, 24, 36, 48, and 60 h). All dosages were administered with a cup, beaker, or syringe (after suspension in 10 ml water) according to body weight: 1 tablet per dose for patients weighing 5 to <15 kg, 2 tablets per dose for patients weighing 15 to <25 kg, and 3 tablets per dose for those weighing 25 to <35 kg. Immediately afterwards, another 10 ml of water was given using the same device. The consumption of food/drink (e.g., breast milk, broth, or sweetened condensed milk) was encouraged following intake of study medication to increase absorption. Patients who vomited a dose within 1 h of treatment received a replacement dose (no more than two doses were to be replaced over the entire treatment phase). For each weight group, an independent computer-generated randomization list was applied. In a first step, approximately 20% of patients (n = 166) were recruited at 4 study centers and formed the control group to perform independent interim analysis to review the interim data for up to 7 days after treatment. Following review of the interim data by an independent data monitoring board, the study was continued on the basis of adequate efficacy and safety results.

Pharmacokinetic and pharmacodynamic assessments. To avoid excessive blood collection in infants or children with malaria, a sparse pharmacokinetic sampling approach was used. We hypothesized that early treatment failures might be related to insufficient exposure to the rapidly acting artemether and/or DHA (as indicated by low maximum concentration in plasma [Cmax values] rather than to low exposure to slow-acting lumefantrine. Therefore, exposure to artemether and DHA was assessed in those patients recruited until the results of the interim analysis indicated adequate treatment response, as measured by Cmax values. For artemether and DHA, these variables included PCTs of ≤24 h, >24 to ≤48 h, or >48 h, presence of parasitemia at day 3, and parasitological outcome at day 7. For lumefantrine, the variables were the 28-day PCR-corrected parasitological cure rate (assessed by PCR genotyping to adjust for reinfections), electrocardiographic (ECG) data, and adverse event (AE) frequencies. Parasite density was determined using Giemsa-stained thick and thin blood films before each intake of study medication during hospitalization and at every follow-up visit (i.e., on days 7, 14, 28, and 42 or on any other day if the child was ill). Two qualified microscopists independently read all the slides, and quality control was performed on a proportion of randomly selected slides. Blood films were considered negative if no parasites were seen in 200 oil-immersion fields in a thick blood film. A 12-lead ECG was recorded at baseline and on day 3 (6 to 10 h after the last dose). Two formulae (Bazett’s and Fridericia’s) were used to calculate corrected QT (QTc) intervals (9). AEs were recorded during hospitalization at the study site and at every follow-up visit.

Statistical evaluation. To explore the relationship between drug exposure and efficacy or safety, quintiles of artemether and DHA Cmax (assessed after first A-L dose) and of the lumefantrine concentrations measured at approximately 6 h after dose 6 were calculated to classify the patients into 5 different exposure classes, which were then descriptively related to efficacy and/or safety variables. For artemether and DHA, these variables included PCTs of ≤24 h, >24 to ≤48 h, or >48 h, presence of parasitemia at day 3, and parasitological outcome at day 7. For lumefantrine, the variables were the 28-day PCR-corrected parasitological cure rate, occurrence of AEs, and QTc changes. To further explore exposure-outcome relationships, statistical models (generalized linear model or correlation model [from Statistical Analysis System software CORR Procedure]) were used whenever appropriate. The pharmacokinetic/pharmacodynamic substudy was explorative in nature; thus, no formal sample size calculation was performed. For the main study, on the basis of an expected cure rate of at least 95% for both treatments and assuming a 10% nonevaluability rate (e.g., loss of follow-up), a sample size of 890 patients (445 per treatment group) was calculated (1).

As prospectively defined in the study protocol, pharmacokinetic parameters were not statistically compared between treatment groups for the following reasons: (i) the Cmax and AUC0–last of lumefantrine have been derived from a population mean concentration–time curve and no estimates of variability for these parameters were available, and (ii) for artemether and DHA Cmax, high interpatient variability was expected, as Cmax shows an inherently larger variation than integrated characteristics such as AUC and Cmax had been determined to be the larger of just two postdose concentration values. In addition, comparison of formulations with identical active ingredients based on statistical significance (P values) might be misleading.

RESULTS

Patients. A total of 899 patients were randomized into the main study: 447 to DT (51.9% males) and 452 to CT (54.6% males), with comparable demographic and baseline characteristics among treatment groups. Mean ± standard deviation (SD) age was 3.7 ± 2.8 years (DT, 3.6 ± 2.7 years; CT, 3.7 ± 2.8 years), and mean ± SD body weight was 14.4 ± 5.5 kg (DT, 14.4 ± 5.5 kg; CT, 14.5 ± 5.5 kg). A total of 60.8% of patients fell into the 5- to <15-kg body weight group, compared to 32.2% in the 15- to <25-kg category and 7.0% in the 25- to <35-kg group. The median parasite density was 29,241 per μl (interquartile range, 10,449 to 67,587 per μl; DT, 26,364 per μl [interquartile range, 11,040 to 59,532 per μl]; CT, 32,288 per μl [interquartile range, 10,050 to 71,274 per μl]) (1). Approximately 90% of patients took the study medication together with a meal. The distribution of meal types was similar between the two formulations (5).

Artemether and DHA plasma concentrations were assessed in 91 patients receiving DT (52, 30, and 9 patients in the 5- to <15-kg, 15- to <25-kg, and 25- to <35-kg groups, respectively) and in 93 receiving CT (56, 29, and 8 subjects in the three body
TABLE 1. C\textsubscript{max} of artemether and DHA per body weight group in pediatric patients treated with a 6-dose regimen of crushed or dispersible artemether-lumefantrine tablets

<table>
<thead>
<tr>
<th>Formulation and parameter</th>
<th>Result by body wt group (dosing regimen)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-&lt;15 kg (6 x 1 tablet)</td>
</tr>
<tr>
<td>Dispersible tablet</td>
<td></td>
</tr>
<tr>
<td>C\textsubscript{max} artemether (ng/ml)</td>
<td>196 ± 204</td>
</tr>
<tr>
<td>C\textsubscript{max} DHA (ng/ml)</td>
<td>62.0 ± 64.8</td>
</tr>
<tr>
<td>Total 3-day dose of artemether (mg/kg body wt)</td>
<td>11.6 ± 2.9</td>
</tr>
<tr>
<td>Crushed tablet</td>
<td></td>
</tr>
<tr>
<td>C\textsubscript{max} artemether (ng/ml)</td>
<td>188 ± 168\textsuperscript{b}</td>
</tr>
<tr>
<td>C\textsubscript{max} DHA (ng/ml)</td>
<td>54.7 ± 58.9</td>
</tr>
<tr>
<td>Total 3-day dose of artemether (mg/kg body wt)</td>
<td>11.1 ± 3.5</td>
</tr>
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\textsuperscript{a} Data are means ± SDs. For the three body weight (dose) groups receiving DT, n = 52, 30, and 9, respectively. For the three body weight (dose) groups receiving CT, n = 56, 29, and 8, respectively, unless indicated otherwise. 
\textsuperscript{b} n = 55.

weight groups, respectively). Lumefantrine plasma concentrations were available from 310 patients treated with DT and 315 patients treated with CT.

Pharmacokinetic results. The mean dose of artemether (per kg body weight) was comparable between body weight groups (Table 1). Similar C\textsubscript{max} values for artemether and DHA for the different body weight groups were obtained following treatment with DT and CT (Table 1). The overall mean ± SD C\textsubscript{max} values for artemether (data for all weight groups pooled) following the first administration of DT and CT were 175 ± 168 and 190 ± 168 ng/ml, respectively; for DHA the values were 64.7 ± 58.1 and 63.7 ± 65.0 ng/ml, respectively. Interpatient variabilities (percent coefficient of variation) for artemether and DHA C\textsubscript{max} were high but within comparable ranges for DT (42 to 105%) and CT (34 to 108%).

For lumefantrine, similar population concentration-time profiles (Fig. 1) and derived pharmacokinetic parameters (Table 2) were obtained following the two treatments. As expected, the highest concentrations were observed after the last (6th) dose of study medication (Fig. 1). The population C\textsubscript{max} (derived from the mean curve shown in Fig. 1) were 6.3 and 7.7 µg/ml after treatment with DT and CT, respectively. T\textsubscript{max} was 66.3 h for both formulations. Pooled AUC\textsubscript{0-last} values were 574 and 636 µg · h/ml for DT and CT, respectively. When the different body weight groups were considered individually, the mean dose of lumefantrine (per kg body weight) was comparable between DT and CT, yielding similar systemic exposure to lumefantrine in both groups (Table 2). In the highest body weight group, the number of patients who contributed data for determining C\textsubscript{max} and AUC\textsubscript{0-last} was too low to allow a reliable interpretation of results. For DT, 17 patients were subject to sparse sampling with 3 samples each available to determine C\textsubscript{max}. For CT, 19 patients participated in the sparse sampling with 1 sample each available for C\textsubscript{max} determination. Thus, these results are not presented.

Pharmacokinetic-pharmacodynamic relationships. (i) Efficacy. In the population as a whole, median PCTs were almost identical between DT (34.3 h) and CT (34.9 h) groups. In the pharmacokinetic substudy, no clinically meaningful correlation was found between the artemether or DHA C\textsubscript{max} and PCT for any of the treatments (Fig. 2). This was supported by results of quintile analyses. Artemether and DHA C\textsubscript{max} values were categorized into 5 quintiles (<48.0, 48 to <113, 113 to <182, 182 to <263, and ≥263 ng/ml for artemether; <15.0, 15.0 to <37.0, 37.0 to <71.0, 71.0 to <98.0, and ≥98.0 ng/ml for DHA), and the predefined efficacy variables were compared across these 5 concentration ranges. When DT and CT data were pooled, no

![FIG. 1. Lumefantrine plasma concentration-time profiles in pediatric patients treated with a 6-dose regimen of crushed or dispersible artemether-lumefantrine tablets (data for the body weight groups are pooled). Dosing occurred under supervised conditions at 0, 8, 24, 36, 48, and 60 h.](image-url)

TABLE 2. Lumefantrine C\textsubscript{max} and AUC\textsubscript{0-last} Per body weight group assessed via sparse sampling in a population of pediatric patients with uncomplicated \textit{P. falciparum} malaria treated with a 6-dose regimen of crushed or dispersible artemether-lumefantrine tablets

<table>
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<tr>
<td>Dispersible tablet</td>
<td></td>
</tr>
<tr>
<td>C\textsubscript{max} (µg/ml)</td>
<td>5.2</td>
</tr>
<tr>
<td>AUC\textsubscript{0-last} (µg · h/ml)</td>
<td>441</td>
</tr>
<tr>
<td>Mean ± SD total 3-day dose of lumefantrine (mg/kg body wt)</td>
<td>68.6 ± 16.9</td>
</tr>
<tr>
<td>Crushed tablet</td>
<td></td>
</tr>
<tr>
<td>C\textsubscript{max} (µg/ml)</td>
<td>6.1</td>
</tr>
<tr>
<td>AUC\textsubscript{0-last} (µg · h/ml)</td>
<td>577</td>
</tr>
<tr>
<td>Mean ± SD total 3-day dose of lumefantrine (mg/kg body wt)</td>
<td>66.7 ± 15.3</td>
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</table>

\textsuperscript{a} One blood sample was taken from each patient at a given time after dose 3, 5, or 6. The numbers of patients in the three body weight (dose) groups for pharmacokinetic analysis were 191, 102, and 17, respectively, for the group receiving CT, NA, not applicable (the number of patients provided too few data to allow reliable interpretation of results).
A descriptive relationship was observed between artemether or DHA $C_{\text{max}}$ (after the first dose) and PCT. There was no major difference between the lowest and highest artemether concentration quintile with regard to PCT. Specifically, the percentage of patients with PCTs of $\leq 24$ h, $>24$ to $\leq 48$ h, and $>48$ h were 18.9%, 70.3%, and 10.8%, respectively, for the lowest artemether quintile and 21.6%, 73.0%, and 5.4%, respectively, for the highest quintile. For DHA these percentages were 16.7%, 75.0%, and 8.3%, respectively, for the lowest quintile and 28.6%, 62.9%, and 8.5%, respectively, for the highest quintile. For both artemether and DHA, there was no presence or persistence of asexual parasites at day 3 in any of the 5 concentration quintiles, and all patients were cured by day 7.

Considering the entire study population, 28-day PCR-corrected cure rates were 97.8% in the DT group and 98.5% in the CT group (1). Due to the very few cases of treatment failure overall and only 1 failure with plasma lumefantrine measured at 6 h after dose 6, no relationship between the lumefantrine $C_{\text{max}}$ and 28-day cure rate could be investigated using quintile analysis. Nevertheless, in those patients with treatment failure and lumefantrine levels available (DT, $n = 3$; CT, $n = 2$), there was a tendency toward lower lumefantrine concentrations (Fig. 3). However, other patients with even lower plasma concentrations were treated successfully (Fig. 3).

(ii) Safety. We failed to find an association between the lumefantrine $C_{\text{max}}$ and the occurrence of treatment-emergent AEs. The mean numbers of treatment-emergent AEs were 2.9 (lowest quintile) and 1.0 (highest quintile), with malaria-related symptoms being the most commonly reported AEs.

Overall, the QTc interval (Bazett’s formula) from baseline to day 3 increased by less than 8 ms, specifically, by a mean of 7.6 ms (SD, 24.9 ms) in the DT group and a mean of 7.1 ms (SD, 24.3 ms) in the CT group. In the pharmacokinetic/pharmacodynamic substudy, linear regression analysis (DT and CT data pooled) suggested a possible association between lumefantrine $C_{\text{max}}$ and QTc prolongation. The association reached statistical significance with Bazett’s formula but not with Fridricia’s formula ($P = 0.036$ [Bazett’s formula]; $P = 0.066$ [Fridricia’s formula]). In contrast, descriptive quintile analysis showed no apparent relationship between lumefantrine $C_{\text{max}}$.
and the increase in QTc from baseline. The lumefantrine concentrations at 6 h after dose 6 were categorized into 5 quintiles (<2.6, 2.6 to <4.5, 4.5 to <6.9, 6.9 to <11, and ≥11.0 µg/ml). The average QTc increase from baseline to day 3 was then calculated within each quintile. The pattern of QTc increases (Bazett’s formula) appeared to be inconsistent across the 5 concentration quintiles (i.e., 9.8, 8.6, 6.2, 8.1, and 11.6 ms). Similar results were seen using Fridericia’s formula (data not shown).

**DISCUSSION**

A pharmacokinetic/pharmacodynamic substudy was performed within a multicenter, investigator-blinded, randomized, noninferiority trial comparing the efficacy and safety of a new pediatric formulation of A-L, dispersible tablet, and the tablet administered crushed in African infants and children with uncomplicated *P. falciparum* malaria. We acknowledge the limitations of a sparse sampling approach for lumefantrine, which allows only an approximation of pharmacokinetic parameters. Moreover, for artemether and DHA, the reported $C_{\text{max}}$ values were derived from 2 values only and may not accurately reflect the true $C_{\text{max}}$ for these substances following oral intake of A-L DT and CT. Finally, $C_{\text{max}}$ comparison is a limited description of the pharmacokinetic features of A-L DT and CT. Nevertheless, the results of our analysis suggest that the dispersible tablet and the tablet administered crushed have similar pharmacokinetic characteristics in the target population. The population plasma concentration-time profile of lumefantrine and the derived parameters $C_{\text{max}}$, $T_{\text{max}}$, and $AUC_{\text{0-\text{last}}}$ were without major differences between the two treatments. Likewise, mean $C_{\text{max}}$ values of artemether and DHA were similar for the two A-L formulations tested. Small numerical differences are not considered clinically relevant. The latter is supported by the clinical efficacy and safety data assessed in the entire study population, which showed that the dispersible formulation was as efficacious as the tablet administered crushed and had a similar safety profile (1).

This is one of the first reports of artemether and DHA exposure data in children with uncomplicated *P. falciparum* malaria treated with A-L. Mean artemether and DHA $C_{\text{max}}$ values observed in this trial (175 and 64.7 ng/ml, respectively, for the dispersible tablet; 190 and 63.7 ng/ml, respectively, for the tablet administered crushed) were in accordance with those reported previously in adult malaria patients from Thailand and Papua New Guinea showing that the lumefantrine plasma level is a key determinant of A-L efficacy (3, 7, 21). In one study conducted in Ugandan children (26.5-kg body weight, on average), the geometric mean lumefantrine $C_{\text{max}}$ was 6.8 µg/ml and the AUC from times zero to 120 h after the last dose amounted to 195 µg · h/ml (19). The lower AUC compared to our analysis can be explained by different sample collection protocols.

The apparent lack of a correlation between artemether and DHA $C_{\text{max}}$ values (after the first A-L dose) and the PCT suggests that with even low initial $C_{\text{max}}$ values, the minimum effective concentration is exceeded and maximal effects are achieved rapidly. Analogous results have been reported for artesunate, another artemisinin derivative (23), where no significant relationships could be shown between parasite clearance and initial plasma concentrations of DHA or artesunate-DHA exposure (using AUC in the first 6 h). A semimechanistic model of parasite dynamics describing the early effect of artemether and DHA concentrations on the parasite density in malaria patients has recently been proposed (10).

In this study, we detected no relationship between lumefantrine exposure and the likelihood of parasitological cure, in particular because of few treatment failures. However, the observed lower-than-average lumefantrine concentrations in the few patients with treatment failure who had pharmacokinetic sampling are in agreement with several reports from studies in Thailand and Papua New Guinea showing that the lumefantrine plasma level is a key determinant of A-L efficacy (8, 12, 16, 22).

The observed absence of a relationship between lumefantrine $C_{\text{max}}$ and the incidence of AEs may be explained by the fact that most commonly reported AEs were symptoms of malaria. The potential relationship between lumefantrine $C_{\text{max}}$ and QTc values was also evaluated in this study. Quintile analysis did not reveal any association, which is in accordance with previous findings showing no relationship between QTc intervals and plasma lumefantrine concentrations (4, 25). The linear regression analysis, however, suggested a possible relationship between lumefantrine $C_{\text{max}}$ and QTc prolongation ($P = 0.036$ [Bazett’s formula]; $P = 0.066$ [Fridericia’s formula]), but the calculated $P$ values should be interpreted with caution, given the exploratory nature of the pharmacokinetic assessments.

In conclusion, the new pediatric formulation of artemether-lumefantrine, dispersible tablet, appeared to provide adequate systemic exposure to artemether, DHA, and lumefantrine in infants and children with uncomplicated *P. falciparum* malaria in Africa, which resulted in the desired clinical outcomes. The use of dispersible tablets may contribute to better treatment outcomes and delay the development of drug resistance.

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