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The effect of food consumption on lumefantrine bioavailability in African children receiving artemether–lumefantrine crushed or dispersible tablets (Coartem®) for acute uncomplicated *Plasmodium falciparum* malaria

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Summary

OBJECTIVES Artemether–lumefantrine (AL) is first-line treatment for uncomplicated malaria in many African countries. Concomitant food consumption may affect absorption of lumefantrine but data in the most important target population, i.e. children, are lacking. Therefore, we evaluated the effect of food intake on oral lumefantrine bioavailability in African children with malaria.

METHODS In a randomised, investigator-blinded, multicentre phase III efficacy trial, 899 infants and children with acute uncomplicated *Plasmodium falciparum* malaria received six doses of AL according to body weight over 3 days either as crushed tablets (Coartem®) or as dispersible tablets. Single blood samples were obtained for lumefantrine plasma concentration determination in a subset of 621 patients, and a two-compartment pharmacokinetic model was constructed.

RESULTS The mean observed lumefantrine plasma concentration for crushed tablet and dispersible tablet, respectively, was 100% and 55% higher with a concomitant meal at the time of dose intake than when taken alone. Similarly, consumption of milk (the most common meal) increased model-estimated lumefantrine bioavailability by 57% (90% CI: 29–96%) with crushed tablets and 65% (90% CI: 28–109%) with dispersible tablets compared to no food. The 28-day PCR-corrected cure rate (primary study endpoint) in the evaluable population was 582/587 [99.1% (95% CI: 98.0–99.7%)] and was not related to food intake.

CONCLUSIONS AL was highly efficacious. Concomitant food intake increased lumefantrine absorption in children with malaria.

keywords lumefantrine, artemether, Coartem, pharmacokinetics, food, bioavailability

Introduction

Despite intensive worldwide efforts to control malaria, almost a million deaths still occur each year, mostly in children aged <5 years (WHO World Malaria Report 2008). The logistical challenges in delivering prompt and effective treatment are compounded by the growing resistance of malaria parasites to conventional therapies. Multidrug resistant forms of *Plasmodium falciparum*, the parasite that causes the majority of malaria-related deaths, are now widespread in parts of Africa, the continent with the highest malaria burden (Roll Back Malaria 2008). As a response to this, new artemisinin-based combination therapies are now globally recommended as first-line treatments for uncomplicated *P. falciparum* malaria. The fixed-dose combination therapy containing artemether and lumefantrine (AL, Coartem®; Novartis Pharma AG, Basel, Switzerland) was pre-qualified by WHO in 2004 and has since then been deployed as first-line therapy in many endemic countries in Africa. AL is highly effective against acute, uncomplicated malaria caused by *P. falciparum* in areas of multidrug resistance (Van Vugt *et al.* 1999, 2000; Lefèvre *et al.* 2001; Piola *et al.* 2005; Falade *et al.* 2005; Mårtensson *et al.* 2005; Makanga *et al.* 2006). AL treatment is recommended to be taken together with food because of enhanced absorption of both artemether and lumefantrine in adult patients (White *et al.* 1999; Ezzet *et al.* 2000). However, the effect of food consumption on lumefantrine pharmacokinetics has never specifically been addressed in African children with malaria, the most important patient group, to whom results obtained in adults of different ethnic background may not necessarily apply.

We report here an analysis of the impact of food consumption on lumefantrine pharmacokinetics and polymerase chain reaction (PCR)-corrected parasitological cure based on data obtained during a multicentre trial in children with acute uncomplicated *P. falciparum* malaria in five African countries (Abdulla *et al.* 2008). This trial included a pharmacokinetic evaluation of artemether [and its metabolite dihydroartemisinin (DHA)] and lumefantrine in patients receiving either the standard crushed tablet of AL or a dispersible formulation, the results of which have already been published (Abdulla *et al.* 2008). The objectives of the current analysis were to determine the relative impact on lumefantrine bioavailability of different foods eaten by patients concomitantly with drug administration in malarial-endemic regions of Africa, and to examine lumefantrine absorption in children who do not consume any food during AL administration. The rate of parasitological cure in subpopulations of patients who did or did not consume food at the time of AL dosing was also recorded.

Methods

Study design and conduct

Pharmacokinetic data were obtained during a randomised, investigator-blinded, multicentre study conducted at eight centres in five countries with endemic malaria (Benin, Kenya, Mali, Mozambique and Tanzania). The study protocol has been described in detail previously (Abdulla *et al.* 2008). Briefly, infants and children with acute uncomplicated *P. falciparum* malaria were recruited following approval from an institutional review board located at each participating centre and from six European and US parent institutions of participating centres (Abdulla *et al.* 2008).

Key inclusion criteria were age ≤12 years, body weight ≥5 kg and <35 kg, presence of fever (axillary or tympanic temperature ≥37.5 °C) or history of fever in the preceding 24 h, *P. falciparum* infection in blood ≥2000/μl and <200 000/μl, and absence of severe and complicated malaria according to the definition of WHO (WHO 2000). Exclusion criteria were haemoglobin <5 g/dl, antimalarial treatment other than chloroquine within the previous 2 weeks, prophylaxis with cotrimoxazole, use of any drug known to influence cardiac function in the preceding 4 weeks, corrected QT interval (QTc) prolongation or any condition known to prolong QTc and AL treatment within the past 30 days.

Patients were randomly assigned to receive AL either as the commercially available tablet (Coartem®), crushed and mixed with a small quantity of water (10 ml), or as the new dispersible tablet formulation which was also administered with 10 ml of water. Each tablet contained 20 mg artemether and 120 mg lumefantrine. Patients received six doses at hours 0, 8, 24, 36, 48 and 60 (i.e. two doses each on study days 0, 1 and 2) according to body weight: one tablet per dose for patients weighing 5.0–14.9 kg, two tablets per dose for those weighing 15.0-24.9 kg and three tablets per dose for patients weighing 25.0–34.9 kg.

Patients were hospitalised during the 3-day treatment phase. All doses of AL were administered under supervision, and intake of food/drink (including breast milk for breast-fed infants) at the time of dosing was encouraged by the investigators but with no specification as to the type or amount of food.

Food consumption

Food intake at the time of dosing was supervised and recorded by the clinical staff member who administered AL. Food was categorised as none, milk or breast feeding (including supplements), liquid (e.g. soup, broth), pancake (e.g. mandazi, fritter), porridge (e.g. groundnut, high

energy protein supplement) or other (specified). All applicable items were checked. The quantity consumed was not recorded.

Pharmacokinetic sample collection and bioanalytics

Because this study was conducted in a very vulnerable population, pharmacokinetic samples were collected in two phases to minimise the burden to the patients. In the first 160 patients enrolled, plasma concentrations of artemether and its major active metabolite DHA were measured to support an interim futility analysis that could determine whether the occurrence of early treatment failures was related to insufficient artemether and/or DHA exposure. Following confirmation at the time of interim analysis that treatment outcome was adequate, the protocol specified that subsequently only lumefantrine plasma concentrations would be measured. In the latter group, a single blood sample was taken from each patient for the assessment of lumefantrine levels to avoid repeated blood samplings. This single sample was taken at one of six possible sampling times, as shown in Table 1. The most frequent time for a blood sample to be taken (50% of patients) was 6 h after the final sixth dose of AL, but sampling times continued to day 14, to take into account the long elimination half-life of lumefantrine.

Blood samples were taken by venepuncture into heparinised tubes. Lumefantrine concentration in plasma was analysed by means of reversed-phase high-performance liquid chromatography method using liquid chromatography–tandem mass spectrometry (LC-MS/MS). The lower limit of quantification (LLOQ) for lumefantrine was 0.05 mg/l; values below this limit were set to 0 in all analyses. Over the calibration range of 0.0499–20 μg/ml, at the LLOQ, the coefficient of variability (% CV) for precision was 3.4% (n = 16) and the percentage bias for accuracy was −0.4% (n = 16). At other concentration levels, the % CV ranged from 2.8% to 4.9% and the bias percentage ranged from −4.5% to 5.4% (n = 16 per level).

Over the quality control range of 0.100 μg/ml to 16 ug/ml, % CV ranged from 3.8% to 6.3% and the bias percentage ranged from −4.7% to 1.3% (n = 18 per level). Plasma analysis was performed centrally by Novartis Pharma S.A.S, Rueil-Malmaison, France.

Table 1 Blood sampling scheme among patients providing samples for lumefantrine measurement. Each patient provided a single blood sample

Sampling time*	6 h after dose 3	6 h after dose 5	6 h after dose 6	Day 3 (24 h after dose 6)	Day 7	Day 14
Time after dose 1 (h)	30	54	66	84	168	336
N (dispersible)	29	30	158	26	31	32
N (crushed tablet)	32	31	163	23	32	30
% Patients	10	10	50	10	10	10

*Two additional patients in each treatment group provided blood samples at other timepoints which were included in the analysis.

Population pharmacokinetic analysis

The pharmacokinetic analysis was undertaken to estimate the relative bioavailability of lumefantrine according to both the type of meal consumed at the time of dosing (e.g. milk *vs.* no food) and the type of AL formulation (crushed *vs.* dispersible tablet). In particular, relative bioavailability was calculated. Relative bioavailability was defined as the ratio of bioavailability [i.e. the area under the concentration–time curve (AUC)] for a particular oral formulation when given with a particular type of meal to that of the reference formulation (crushed tablet) and the reference meal type (no food). A population pharmacokinetic analysis data set was constructed from actual date and time of dosing, and sampling events.

Data on the blood concentration of lumefantrine from each of the single samples collected from patients receiving either crushed and dispersible tablets were first fitted separately and then pooled to characterise model-based relative differences in bioavailability attributable to the type of meal and formulation. In the model, clearances and volumes were allometrically scaled by body weight to the exponents 0.75 and 1.0, respectively (Anderson & Holford 2008). The effects of age on bioavailability were also explored. The likelihood function and diagnostic plots were used to assess goodness of fit and to refine model assumptions. PROC NLMIXED (SAS Release 8.2 on AIX 5.2 platform) was used to fit each model. Examination of standardised residuals from the final model *vs.* age, gender, baseline parasite count, treatment, weight, country, baseline body temperature indicated no reason to adjust the model according to these variables.

Based on the final model, 90% confidence intervals (CIs) on the model-based relative bioavailability for comparing meal types and formulations were constructed by PROC NLMIXED and by the bootstrap method. The endpoints for the bootstrap CI were computed as the 5th and 95th percentiles of parameter estimates from 399 bootstrap samples where each bootstrap sample was stratified by treatment to include the same number of patients in the crushed treatment arm and dispersible treatment arm as used in the model.

Confidence intervals for 28-day PCR-corrected cure rates were computed using the Clopper–Pearson method and F distribution (Newcombe 1998).

Results

Patient population

In total, 899 patients were randomised during the study, of whom 452 (50.3%) received the crushed tablet. Blood samples for determination of lumefantrine concentration were obtained from 625/739 patients (84.6%) enrolled after the interim analysis. One patient assigned to the dispersible tablet group had no recorded date and time of sample collection. Three patients (one in the dispersible group and two in the crushed tablets group) whose samples were drawn on day 14 had lumefantrine concentrations that were more than 100-fold times the LLOQ when other patients had levels typically near or below the LLOQ, there was no known reason for this. As a result of these discrepancies, these four outliers were excluded from the pharmacokinetic analysis population, which thus comprised 621 patients (308 dispersible, 313 crushed tablet).

In the pharmacokinetic analysis population, mean age was 4.1 ± 2.7 (median 3.4, range 0.25–12.4 years), 322 patients (51.9%) were men, and mean body weight was 14.4 ± 5.3 kg (median 13.1, range 5.0–34.0 kg). Patient demographics for this subpopulation were similar to the total study population and between groups receiving dispersible or crushed tablets (data not shown). The number of patients included in the pharmacokinetic analysis population from Benin, Kenya, Mali, Mozambique and Tanzania, respectively, was 105, 135, 86, 97 and 198. Mean parasite count (asexual forms) at enrolment was 48 000/μl (median 29 000/μl, range 500–629 000/μl). Mean body temperature was 38.1°C (median 38.0 °C, range 35.6–41.5 °C). Of the 621 patients included in the pharmacokinetic analysis, one patient received only two doses of AL and the remainder received the full six-dose treatment course. Thus, the total number of AL dosing events used in the model was $6 \times 620 + 2 = 3722$.

Food intake

Information on food intake was recorded for all 3722 doses. The predominant meal types were milk alone (57.4%), pancake alone (27.8%) and none (9.6%). These accounted for 94.8% of intake during the treatment phase. The distribution of meal types was similar between the two formulations (Table 2).

Lumefantrine pharmacokinetics

Overall, the mean observed lumefantrine concentration was 5.0 mg/l (n = 621). To assess the effect of food, the mean observed concentration was then calculated for only those patients who ate at the time of the last dose prior to collection of the pharmacokinetic blood sample. For the 550 patients who ate at the time of their last dose, the mean observed lumefantrine concentration was 5.3 mg/l. For the 71 patients who consumed no food at the time of their last dose prior to pharmacokinetic sampling collection, the mean observed lumefantrine concentration was 3.0 mg/l. With a concomitant meal at the time of the dose prior to pharmacokinetic sampling, mean observed lumefantrine plasma concentration was higher compared to no meal for both the dispersible and crushed tablet formulations (dispersible tablet, 4.8 mg/l (n = 277) with food *vs.* 3.1 mg/l (n = 31) without food, P = 0.003; crushed tablet, 5.8 mg/l (n = 273) with food *vs.* 2.9 mg/l (n = 40) without food, $P < 0.001$). When comparisons of food *vs.* no food at the time of each dose were broken down further by the sampling time and formulation, the sample sizes became small (n = 2 to n = 5) in the 'no food' category except for the 6-h sample after dose 6, where 50% of the samples were scheduled for collection. However, in spite of

Table 2 Food intake at or near the time of artemether–lumefantrine (AL) dosing. Information for all six AL doses are shown

	Dispersible tablet [n = 308 (1848 doses)]	Crushed tablet [n = 313 (1874 doses)]	Total [n = 621 (3722 doses)]
No food	171 (9.3%)	187 (10.0%)	358 (9.6%)
Milk alone	1066 (57.7%)	1069 (57.0%)	2135 (57.4%)
Pancake alone	520 (28.1%)	516 (27.5%)	1036 (27.8%)
Porridge alone	68 (3.7%)	74 (3.9%)	142 (3.8%)
Soup alone	1 (0.1%)	4 (0.2%)	5 (0.1%)
Other	21 (1.1%)	23 (1.2%)	44 (1.2%)
Milk + other	1 (0.1%)	1 (0.1%)	2 (0.1%)
Total doses administered	1848 (100.0%)	1874 (100.0%)	3722 (100.0%)

the small sample sizes, concentrations remained consistently higher in children with concomitant food intake compared to non-fed children in 11 of 12 cases (Figure 1).

The relative bioavailability of lumefantrine for the dispersible tablet compared to the crushed tablet was 0.93 (bootstrap 90% CI: 0.69–1.25) without consumption of food (Table 3). Concomitant food intake increased bioavailability of lumefantrine regardless of formulation (Figure 2). For a hypothetical 3.5- year-old child, consumption of milk or pancake increased bioavailability compared to no food by a factor ranging from 1.57 to 2.74 depending upon meal type and formulation. Specifically, consumption of milk increased lumefantrine bioavailability by 1.57 (bootstrap 90% CI: 1.29–1.96) *vs.* no food in children receiving the crushed tablet (Table 3). The relative bioavailability of lumefantrine for the dispersible tablet compared to the crushed tablet was 0.98 (bootstrap 90% CI: 0.84–1.11) with the consumption of milk.

When given a concomitant meal, regardless of formulation, older children had increased bioavailability compared to younger children (Figure 3). Among children who consumed food with their dose, a doubling of

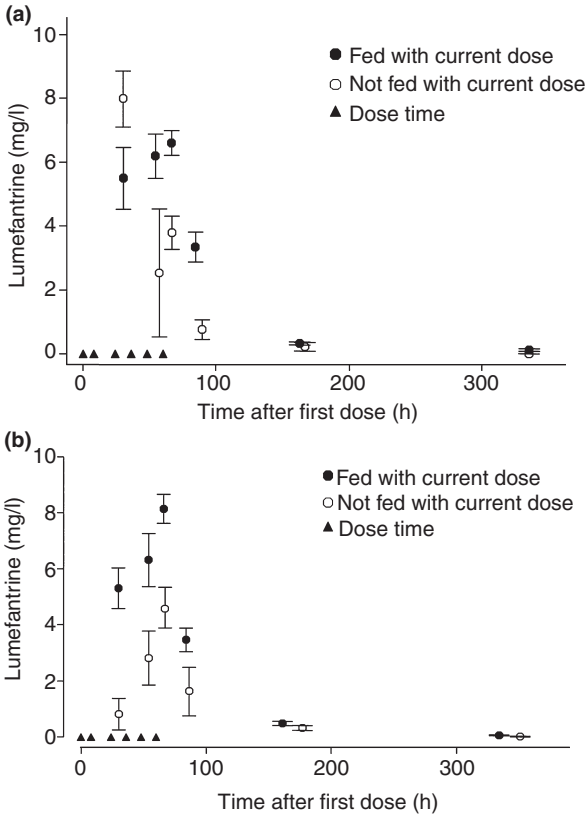

Figure 1 Observed lumefantrine concentrations for patients receiving (a) dispersible (b) crushed tablet according to whether food was consumed at time of dose or not. Values shown are mean ± SE. The number of samples for the 'not fed' group was 3, 2, 17, 3, 3, and 3 for dispersible tablet and 2, 4, 21, 3, 5, and 5 for crushed tablet, respectively, at the following sampling points: 6 h after dose 3, 6 h after dose 5, 6 h after dose 6, day 3 (24 h after dose 6), day 7 and day 14. The number of samples for both formulations in the 'fed' group was approximately eight times as great as in the 'not fed' group and showed similar distribution across sampling times.

Table 3 Model-based relative lumefantrine bioavailability comparisons of meal type *vs.* not fed according to artemether–lumefantrine formulation

Formulation	Food intake	Relative bioavailability	Bootstrap 90% CI
Crushed tablet	Milk *vs.* not fed	1.57	1.29, 1.96
	Pancake *vs.* not fed	2.74	1.93, 3.61
Dispersible tablet	Milk *vs.* not fed	1.65	1.28, 2.09
	Pancake *vs.* not fed	1.83	1.42, 2.39

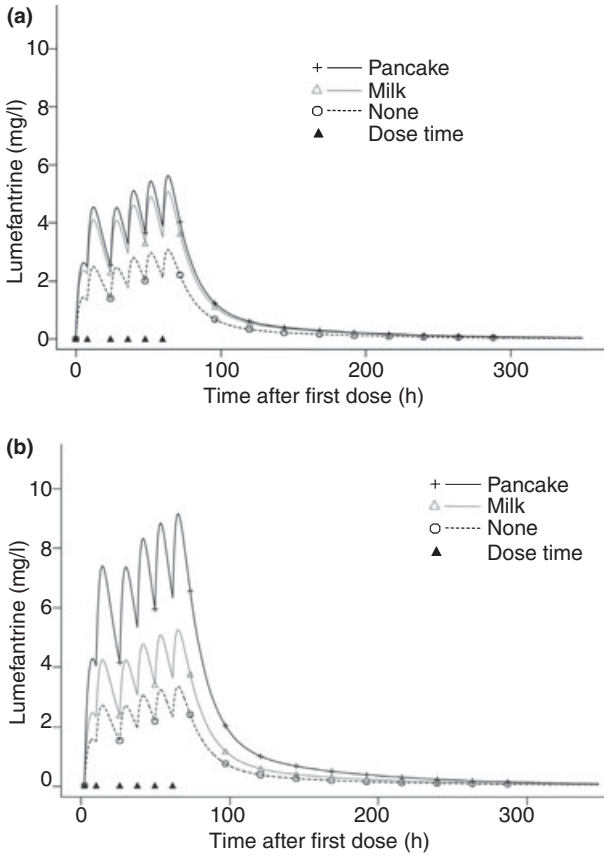

Figure 2 Predicted plasma lumefantrine concentration *vs.* time after first dose by treatment and meal type for (a) dispersible (b) crushed tablets.

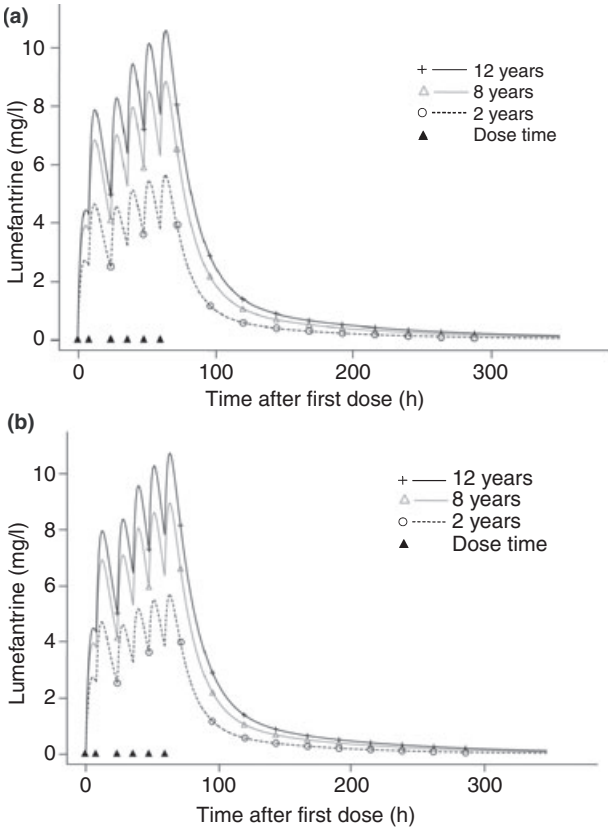

Figure 3 Predicted plasma lumefantrine concentration *vs.* time after first dose for children aged 2, 8, and 12 receiving milk for (a) dispersible (b) crushed tablets. The concomitant meal was assumed to be milk with each dose. Age 2 was simulated as 10 kg body weight and 120 mg lumefantrine dose; age 8 was simulated as 20 kg body weight and 240 mg lumefantrine dose; age 12 was simulated as 30 kg body weight and 360 mg lumefantrine dose.

post-conceptional age (PCA) resulted in an increase in bioavailability of $2^{0.281} = 1.22$ (bootstrap 90% CI: 1.13–1.29). All children were assumed to have had a near full-term birth. Consequently, for example, an age of 0.75 years was transformed to a PCA of 1.5 years. The 22% increase pertained to any doubling of PCA across the age range of the study. Thus, for example, the estimate of bioavailability for a patient whose PCA was 12 years was 22% more than a patient whose PCA was 6 years. When given a concomitant meal, this resulted in a factor of $(2^{0.281})^4 = 2.18$, or approximately a doubling in lumefantrine bioavailability across the age range in the study. The age effect was not observed in children without concomitant food intake, but patient numbers in this group were small (data not shown).

The relationship between predicted lumefantrine AUC and efficacy was also assessed using the pharmacokinetic model. Among patients in the primary analysis population who completed the full six-dose treatment course, mean AUC predicted by the model (summed across all six doses) was similar in those who achieved 28-day PCR-corrected parasitological cure [553 ± 220 h × mg/l (n = 797)] or did not achieve cure [563 ± 216 h × mg/l (n = 13)].

Efficacy outcomes

In the trial within which this pharmacokinetic analysis was performed, the primary efficacy outcome was the 28-day PCR-corrected parasitological cure. Of the 621 patients in the pharmacokinetic population, 587 met the criteria for inclusion in primary efficacy analysis (i.e. patients who completed 28 days in the study with a valid parasitological assessment or were classified as treatment failure by day 28 as a result of discontinuation of study drug and administration of rescue treatment). The 28-day PCR-corrected cure rate was 582/587 (99.1%, 95% CI: 98.0–99.7%). Results were similar to the dispersible and crushed tablet formulations: 286/289 (99.0%, 95% CI: 97.0–99.8%) and 296/298 (99.3%, 95% CI: 97.6–99.9%), respectively. Treatment failure occurred in five patients, of whom all completed the full six-dose course of AL therapy with some meal at every dose. Reassuringly, even patients who consumed no food near the time of all their AL doses (35/587; 6.0%) still achieved 28-day PCR-corrected cure (100%; 95% CI: 90.0%–100%).

Discussion

Our findings, derived from the largest pharmacokinetic study of AL undertaken in a paediatric population, confirm that consumption of milk or regional diets during treatment leads to an increased exposure to lumefantrine in children with malaria. Estimates of the relative increase in lumefantrine exposure ranged from 1.57 to 2.74 for predominant meal types (milk or pancakes) across drug formulations when compared to no meal. Encouragingly, PCR-corrected parasitological cure was achieved in all 35 patients who were unable to eat food at the time of any dose. However, to optimise efficacy, food intake should preferably be resumed as soon as possible in view of observations, in adult patients from the north west border of Thailand, of an association between lumefantrine exposure and clinical and parasitological outcomes (Price *et al.* 2006).

The relative effect of concomitant food on lumefantrine pharmacokinetics observed in our analysis is consistent with that reported by Ezzet *et al.* (2000) in a double-blind

trial of 266 mainly adult patients with uncomplicated *P. falciparum* malaria in Thailand. In this study, patients received one of three AL regimens (four doses over 3 days, or six doses over 3 or 5 days), but data on the effect of food was analysed for the whole population combined. Their pharmacokinetic model estimated that lumefantrine oral bioavailability increased by 48% after a light meal and by 108% after a normal meal compared to liquids only. These differences were statistically significant. In our population, the relative increase in exposure between patients consuming milk or a solid meal (pancakes) compared to no food was in a similar range for the crushed tablet (57–174%) and the dispersible tablet (65–83%).

The cure rate in our study was high (98.2%) and there was no tendency for lower food intake in the few patients in whom treatment failure was recorded. Interestingly, Piola and colleagues have compared the PCR-corrected cure rates of AL following supervised and unsupervised drug administration in children up to 14 years (Piola *et al.* 2005). In the children randomised to supervised AL dosing, their fat intake was ensured by a meal containing ~23 g fat (300 ml milk and 30 g peanuts) or breast milk. The unsupervised group were given the first dose of AL at the clinic and then discharged with advice to take treatment with fatty meals or breast milk. The 28-day PCR-corrected cure rate in evaluable patients was 100% in both groups despite the fact that a pharmacokinetic substudy revealed that lumefantrine plasma concentration was significantly higher in the supervised group (Checchi *et al.* 2006). The identical efficacy results are consistent with the suggestion that a standard African diet is sufficient to achieve adequate lumefantrine exposure and maximise efficacy (Premji *et al.* 2008).

We observed increased lumefantrine absorption in older children *vs.* infants when AL was administered with food. It is possible that dosing by weight may produce lower exposure in smaller children, but greater food intake by older children may also have influenced absorption patterns, as could a higher rate of vomiting in younger children, as neither the volume of food nor occurrence of vomiting were accounted for in the model. No effect of age was detected in the cohort of children who took no food, but as there were few patients in this group, this finding would need to be confirmed.

The current analysis did not include the effect of food consumption on blood concentrations of artemether or DHA. While potentially useful, the impact of food on bioavailability of artemether is markedly lower than for lumefantrine (Lefèvre & Thomsen 1999). Moreover, area under the lumefantrine plasma concentration–time curve (AUC) is the principal determinant of the probability of cure in acute falciparum malaria under AL treatment (Ezzet *et al.* 1998). Importantly, the pharmacokinetic data set included a substantial number of patients, which permitted meaningful comparisons between the three main consumption groups (milk, pancakes and no food). However, we did not record the amount of food or milk consumed, or the protein/fat/carbohydrate content, or the total energy intake, which may have provided a better quantification of the relationship of food intake and bioavailability. Also, hospitalisation and ongoing recommendations from clinical staff to consume food or milk may have artificially increased intake, particularly during the early stages of the disease, and hence, enhanced the efficacy of AL treatment. This could also have accentuated the differences between the fed and non-fed children and overestimated lumefantrine exposure in routine practice. We are also aware that by taking a single blood sample from each patient, we cannot take into account the effect of earlier food intake – or fasting – on bioavailability of previous doses, which could exert an effect on the lumefantrine blood concentration at the time of sampling. Ethically, however, it was not considered acceptable to take multiple blood samples from children who were ill with malaria. Lastly, the pharmacokinetic modelling did not take into account a possible effect of vomiting, a frequent symptom of malaria. The rate of vomiting, however, was similar in both the dispersible and crushed tablet groups (7% and 9%) so is unlikely to have influenced the between-group comparisons.

In conclusion, consumption of milk or typical African food enhances lumefantrine absorption and, as shown here in a setting where no specific recommendations were made regarding the type of volume of food, provides adequate exposure without the need of a particularly high-fat meal. Consumption of food at the time of AL dosing remains advisable.

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