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C. Falade
University of Ibadan

M. Makanga
Kenya Medical Research Institute

Zul Premji
Aga Khan University, zul.premji@aku.edu

C.E. Ortmann
Novartis Pharma AG

M. Stockmeyer
Novartis Pharma AG

See next page for additional authors

Authors
C. Falade, M. Makanga, Zul Premji, C.E. Ortmann, M. Stockmeyer, and P. Ibarra de Palacios

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Efficacy and safety of artemether—lumefantrine (Coartem®) tablets (six-dose regimen) in African infants and children with acute, uncomplicated falciparum malaria

Catherine Falade[a], Michael Makanga[b], Zul Premji[c,*], Christine-Elke Ortmann[d], Marlies Stockmeyer[d], Patricia Ibarra de Palacios[d]

[a] *Malaria Research Laboratories, IMRAT, College of Medicine, University of Ibadan, Ibadan, Nigeria*
[b] *Kenya Medical Research Institute, Kilifi, Kenya*
[c] *Muhimbili University College of Health Sciences, Dar es Salaam, Tanzania*
[d] *Novartis Pharma AG, Basel, Switzerland*

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Summary Approximately one million children die from malaria each year. A recently approved artemisinin-based tablet, Coartem (co-artemether), comprising artemether 120 mg plus lumefantrine 20 mg, given in four doses, provides effective antimalarial treatment for children in many sub-Saharan countries. However, this regimen is considered insufficient for non-immune infants and in areas where multidrug-resistant *Plasmodium falciparum* predominates. This open-label study assessed the efficacy and safety of co-artemether administered to 310 African children weighing 5—25 kg, with acute, uncomplicated falciparum malaria. Six doses of co-artemether were given over 3 days, with follow-up at 7, 14 and 28 days. Treatment rapidly cleared parasitemia and fever. The overall 28-day cure rate was 86.5%, and 93.9% when corrected by PCR for reinfection. Cure rates at 7 and 14 days exceeded 97.0% (uncorrected) and, on day 28, were similar in infants (5—<10 kg) previously exposed to malaria infection (partially immune: 88.6% uncorrected; 93.3% corrected), and in those who were non-immune (82.5% uncorrected; 95.0% corrected). Adverse events were mostly mild. There was no electrocardiographic evidence of cardiotoxicity. The co-artemether six-dose regimen, treating acute uncomplicated falciparum malaria in African children, achieved rapid parasite clearance and a high cure rate. Treatment was generally safe and well tolerated.

* Corresponding author. Tel.: +255 22 2153419; fax: +255 22 2150465.
E-mail address: zpremji@muchs.ac.tz (Z. Premji).

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1. Introduction

Malaria is the world's most important parasitic disease, especially when *Plasmodium falciparum* is the causative agent. Most of the burden of falciparum malaria is borne by small children in sub-Saharan Africa. Although most cases are uncomplicated, falciparum malaria can evolve into a severe, complicated and potentially fatal form, especially in young children. Malaria kills approximately one million children each year (Fischer and Bialek, 2002).

In many regions of the world, malaria parasites have become unresponsive to conventional antimalarial drugs. Many antimalarial drugs have been associated with unsatisfactory efficacy, tolerability and safety profiles, as well as complicated and expensive dosage regimens. Consequently, there is an urgent need for new antimalarial drugs that are effective, safe and affordable.

This study was designed, in partnership with the WHO, to assess the efficacy, safety and tolerability of the only artemisinin-based, fixed-combination tablet of two drugs (20 mg artemether and 120 mg lumefantrine [co-artemether, Coartem®]) in African infants and children, with a bodyweight as low as 5 kg, suffering from acute, uncomplicated falciparum malaria. The co-formulation of an artemisinin derivative combined with another antimalarial drug was designed to improve efficacy and compliance, and minimize selection of drug-resistant parasite strains (White and Olliaro, 1996). Artemisinin derivatives are considered to be an integral part of the 'Roll Back Malaria' partnership (WHO, 2000). Artemether was used in this study because it exerts rapid schizontocidal effects. However, the agent is rapidly eliminated (Lefèvre and Thomsen, 1999), and recrudescence occurs frequently when artemether is given alone for less than 7 days (Bunnag et al., 1991). Artemether was therefore combined with lumefantrine, which has a much longer half-life, producing a low recrudescence rate (Ezzet et al., 1998). Co-artemether is designed to provide a rapid onset of action, a long duration of effect and a high cure rate. As co-artemether is a fixed combination and is effective when given in a 2- or 3-day regimen, compliance is likely to be improved as compared with free combinations of loose tablets requiring longer treatment periods.

The four dose regimen of co-artemether has been shown to be effective, in terms of the 28-day cure rate, in regions where *P. falciparum* is not multidrug-resistant and patients are partially immune (Kshirsagar et al., 2000). However, in areas where the parasite is drug-resistant, a six-dose schedule is required to produce similar cure rates. Studies in Southeast Asia where plasmodial resistance to antimalarial drugs is common, have shown that the six-dose regimen is more effective than the four-dose regimen, while remaining equally safe and well tolerated (Lefèvre et al., 2001; Van Vugt et al., 1999, 2000). While the four-dose regimen has been used safely and effectively in children of all ages, the six-dose regimen has, to date, only been used in studies of children weighing more than10 kg (Lefèvre et al., 2001).

The primary aim of the study was to assess the safety of a six-dose regimen (6 or 12 tablets) of co-artemether administered for 3 days to patients under 10 years of age weighing 5—25 kg, suffering from acute, uncomplicated falciparum malaria. The secondary objective was to assess the efficacy of this regimen, particularly for non-immune infants (5—<10 kg).

2. Materials and methods

2.1. Study design

No existing medication was approved for a direct comparison, so an open-label, non-comparative, multicenter study was used. Hospitalized children (5—25 kg) in three centers (in Kenya, Nigeria and Tanzania) were allocated to one of three bodyweight groups: 5—<10 kg (infants) or 10—<15 kg, each given six doses of one co-artemether tablet; or 15—25 kg, each given six doses of two co-artemether tablets. Key inclusion criteria were: microscopy-confirmed *P. falciparum* malaria with parasitemia of 1000—100 000 parasites/mm^3; fever ($\geq$37.5 °C); and bodyweight of 5—25 kg. Key exclusion criteria were: severe malaria or danger signs of severe malaria; other *Plasmodium* infection; use of any drug known to influence cardiac function (e.g. halofantrine) within four weeks before screening; and requirement for continuation of other treatment for malaria.

Doses were administered, under nurse or doctor supervision, at 0, 8, 24, 36, 48 and 60 hours. Tablets were given with food or drink (preferably milk) whenever possible. In children who were unable to swallow tablets, the tablets were crushed and suspended in sterile water for dosing. Clinical evaluations, including parasite counts, were made at 8 hours then on days 1, 2, 3, 7, 14 and 28. Boys and non-menarche girls (5—25 kg) suffering from acute, uncomplicated *P. falciparum* malaria (confirmed microscopically by Giemsa-stained thick

film; 10^3—10^5 parasites/mm^3) were included if their axillary temperature exceeded 37.5 °C.

Malaria transmission intensity is considered high at each of the three study sites. In Nigeria, the study was conducted in Ibadan, a hyperendemic area where malaria transmission occurs all year round, with a major peak during the rainy season (June—September) (Salako et al., 1990). In Tanzania, the study was conducted at Kisarawe District Hospital on the East Coast in a rural area considered holoendemic for malaria transmission as well as at Kilifi in Kenya where the average incidence is about 1.5 to 2 episodes of malaria per year (Nyakeriga et al., 2004).

The Institutional Review Board of the respective study centers and the Scientific Committee on Research in Human Subjects of the WHO reviewed and approved the study protocol. The study ensured adherence to Good Clinical Practice and was carried out in accordance with the Declaration of Helsinki and directives regarding the rules governing medicinal products in the European Community and the United States Code of Federal Regulations dealing with clinical studies.

2.2. Discontinuation of treatment

Adverse events, unsatisfactory therapeutic effect, loss of patient to follow-up, patient noncompliance or consent withdrawal were criteria for discontinuation. All discontinued patients were followed-up for 28 days for safety assessments, where possible.

2.3. Rescue treatment

If vomiting of the replacement dose (of a vomited initial dose) within 2 hours of its intake occurred, study treatment was stopped and rescue treatment (with a locally effective antimalarial drug such as amodiaquine) was used.

2.4. Efficacy assessments

Treatment efficacy was determined based on parasitological cure rates at days 7, 14 and 28, by the times to parasite and fever clearance; and from the proportion of patients without gametocytes.

Recrudescence denoted clinical recurrence of malaria after the initial clearance of parasites from the circulation. Parasite reappearance was interpreted as either true recrudescence (with relapse caused by the same parasite) or a new infection, depending on PCR analysis (Henning et al., 1999; Snounou and Beck, 1998). Thus, treatment efficacy for cure rates are described as uncorrected or corrected.

2.5. Safety assessments

All adverse events were monitored and recorded. Treatment-emergent symptoms of malaria were defined as adverse events occurring anew or worsening from baseline, but occurring before recurrence of parasitemia.

2.6. Safety evaluation

Assessment of possible treatment-related adverse events during acute disease is difficult, due to the background dominance of malaria-related signs and symptoms. Malaria clinical features were therefore recorded at baseline, during treatment, and during the three follow-up visits.

2.7. Electrocardiogram evaluation

A standard 12-lead electrocardiogram, including QTc interval as the principal measure, was qualitatively analyzed at baseline and on day 3. Both primary data and changes from baseline were derived from an independent, blinded review of electrocardiographic results. Corrected QTc interval values were calculated according to Bazett's formula ($QTc = QT/\sqrt{RR}$) and Fridericia's formula ($QTc = QT/\sqrt[3]{RR}$ msec) and, for males and females respectively, were classified as normal (<430 and <450 msec), borderline (431—450 and 451—470 msec) or prolonged (>450 and >470 msec).

2.8. Statistical methods

Data from the three centers were combined, analyzed and summarized for patients in the three bodyweight groups, after completion of the 28-day trial period. Safety and intention-to-treat (ITT) populations included all patients who had received at least one dose of co-artemether. The per protocol (PP) population comprised ITT patients who received all six doses of medication and who adhered to the study protocol.

All efficacy analyses were performed on the ITT population, with supportive analyses on the PP population. For each cure rate (at days 7, 14 and 28), the simple proportion of cured patients and 95% confidence intervals were calculated using exact Pearson—Clopper limits. For time to parasite and fever clearance, the median and 95% confidence intervals were calculated using the Kaplan—Meier

method. The influence of selected baseline characteristics on cure rates was evaluated by a logistic regression analysis modeling failure. Cox's proportional hazard regression analysis was performed to evaluate the time to parasite and fever clearance.

3. Results

3.1. Patient disposition and demographic data

In total, 310 patients were enrolled in the study (ITT population). The distribution of patients between study sites was: Kenya 107 patients, Nigeria 103 patients, and Tanzania 100 patients. Four patients discontinued treatment prematurely, one due to an adverse event (urticaria), two withdrew consent, and one due to a protocol violation. Three patients completed treatment but discontinued follow-up; one died of gastroenteritis and two were lost to follow-up (Table 1).

Major protocol violations were recorded in 19 children for the following reasons: at least one missing parasite count ($n = 7$); fewer than six doses of study medication taken ($n = 4$); other antimalarial medication taken during the study ($n = 4$); parasite counts $<10^3$ or $>1.4 \times 10^5/mm^3$ at baseline ($n = 3$); and no replacement dose given after vomiting within 2 hours of dosing ($n = 1$).

The gender distribution was approximately equal for the ITT population and for each bodyweight group (Table 1). Almost all the patients (306/310, 99%) received the full, six-dose course of co-artemether treatment. Vomiting was uncommon and occurred most frequently in the infant group (5—<10 kg, 22/154, 14.3%). Most of the children who vomited did so after only a single dose. Only two infants (0.6%) required rescue medication because of vomiting of the drug. In total, 34/310 (11%) of the patients required further treatment

Table 1 Patient disposition and demographic data (intention-to-treat population)

	Bodyweight group			Total
	5—<10 kg	10—<15 kg	15—≤25 kg	
Patients: *n* (%)				
Enrolled and treated	154 (100)	110 (100)	46 (100)	310 (100)
Discontinued treatment	3 (1.9)	1 (0.9)	0	4 (1.3)
Discontinued during follow-up	1 (0.6)	2 (1.8)	0	3 (1.0)
Study site: *n* (%)				
Kenya	54 (35.1)	38 (34.5)	15 (32.6)	107 (34.5)
Nigeria	50 (32.5)	37 (33.6)	16 (34.8)	103 (33.2)
Tanzania	50 (32.5)	35 (31.8)	15 (32.6)	100 (32.2)
Sex: *n* (%)				
Male	77 (50.0)	60 (54.5)	24 (52.2)	161 (51.9)
Female	77 (50.0)	50 (45.5)	22 (47.8)	149 (48.1)
Age (years)				
Median	1.1	2.8	6.1	2.0
Range	0.2—3.1	0.8—6.8	2.9—9.9	0.2—9.9
Bodyweight (kg)				
Median	8.3	12.0	18.0	10.0
Range	5.0—9.9	10.0—14.5	15.0—25.0	5.0—25.0
Immune status: *n* (%)				
Partial	105 (68.2)			
Non-immune	40 (26.0)			
Immune	8 (5.2)			
Unavailable	1 (0.6)			
Parasite density (no./mm^3)				
Median	17 581	20 929	14 726	18 488
Range	1080—100 000	1373—137 760	1000—104 919	1000—137 760
Body temperature (°C)				
Median	38.5	38.5	38.8	38.5
Range	37.5—40.9	37.5—40.9	37.6—40.1	37.5—40.9

because of parasite recurrence; the majority (26/310, 8.4%) received amodiaquine.

3.2. Cure rates with co-artemether

Both 7- and 14-day uncorrected cure rates were greater than 97% for the ITT population (Table 2), and attained 100% for the PP population in all bodyweight groups. The overall 28-day cure rate for the ITT population, corrected for reinfection, was 291/310 (93.9%).

Between days 14 and 28, malaria became evident again in 34/310 (11%) children. New infections, distinguished from true recrudescence by the PCR findings, developed in 23/310 (7.4%) and true recrudescence was documented in 11/310 (3.5%). Cure rates were independent of baseline parasite densities, body temperature, study site, age, sex, bodyweight (despite the relatively higher mg/kg doses received by the 5—<10 kg group), or previous malaria infection.

3.3. Times to parasite and fever clearance

The median times to parasite clearance ranged from 24 to 36 hours. An exploratory analysis (Cox's proportional hazard regression) showed that there was no statistically significant effect of baseline parasite density, body temperature, age, sex, bodyweight or previous malaria infection on parasite clearance rates. Overall, 170/305 (55.7%) patients achieved clearance within 24 hours, and 302/307 (98.4%) within 48 hours. The median time to fever clearance was less than 8 hours in all groups; 233/310 (76%) of the children took acetaminophen (paracetamol) during the study.

Only a very low proportion of patients, 26/310 (8.4%), had gametocytes on days 0—3. None of the children had gametocytes after day 14.

Symptoms of malaria disappeared in almost all patients during the first three days of the study.

3.4. Efficacy in non-immune infants

The malaria immunity status of infants weighing 5—<10 kg was assessed before the start of treatment. An infant was considered partially immune if he/she lived in an endemic area with high prevalence of malarial infection, or had suffered a previous attack of malaria; otherwise, infants were considered to be non-immune. Forty of the 154 infants (26%) had not suffered from a known previous malaria infection, and were considered to be non-immune at baseline. Uncorrected cure rates for days 7 and 14 in these non-immune infants (5—<10 kg) were 100.0%. The 28-day uncorrected cure rate was 82.5% (33/40), compared with 88.6% (93/105) in partially immune infants. When corrected by PCR results, the 28-day cure rate for the ITT non-immune population was 95.0% (38/40), compared with 93.3% (98/105) for the partially immune ITT population.

3.5. Adverse events

The most common adverse events, irrespective of cause, reported in >10% of the patients overall included cough, anemia, anorexia, vomiting and

Table 2 Parasitological cure rates

Population	Bodyweight group			Total
Cure rate	5—<10 kg (n =154)	10—<15 kg (n = 110)	15—≤25 kg (n = 46)	(n = 310)
ITT population				
7-day	152/154 (98.7%)	108/110 (98.2%)	46/46 (100%)	306/310 (98.7%)
14-day	151/154 (98.1%)	107/110 (97.3%)	45/46 (97.8%)	303/310 (97.7%)
28-day	133/154 (86.4%)	94/110 (85.5%)	41/44 (89.1%)	268/310 (86.5%)
ITT population, PCR corrected				
7-day	152/154 (98.7%)	108/110 (98.2%)	46/46 (100.0%)	306/310 (98.7%)
14-day	151/154 (98.1%)	107/110 (97.3%)	45/46 (97.8%)	303/310 (97.7%)
28-day	145/154 (94.2%)	103/110 (93.6%)	43/46 (93.5%)	291/310 (93.9%)
PP population				
7-day	144/144 (100%)	105/105 (100%)	44/44 (100%)	293/293 (100%)
14-day	144/144 (100%)	105/105 (100%)	43/43 (100%)	292/292 (100%)
28-day	127/143 (88.8%)	92/105 (87.6%)	39/43 (90.7%)	258/291 (88.7%)

Table 3 Adverse events (after baseline but before recurrence) occurring in more than 10% of patients treated with co-artemether, irrespective of cause

Adverse event	Bodyweight group			Total
	5—<10 kg	10—<15 kg	15—≤25 kg	
Patients: *n* (%)	154 (100)	110 (100)	46 (100)	310 (100)
Cough	44 (28.6)	28 (25.5)	5 (10.9)	77 (24.8)
Anemia	41 (26.6)	21 (19.1)	9 (19.6)	71 (22.9)
Vomiting	25 (16.2)	12 (10.9)	8 (17.4)	45 (14.5)
Anorexia	17 (11.0)	15 (13.6)	5 (10.9)	37 (11.9)
Diarrhea	20 (13.0)	10 (9.1)	3 (6.5)	33 (10.6)
Hepatomegaly	10 (6.5)	12 (10.9)	5 (10.9)	27 (8.7)
Splenomegaly	11 (7.1)	13 (11.8)	2 (4.3)	26 (8.4)
Upper respiratory tract infection	19 (12.3)	6 (5.5)	0 (0)	25 (8.1)

diarrhea (Table 3). Some differences in adverse events were seen between bodyweight groups but, since these were generally mild, differences were not considered to be clinically significant. In total, 76/310 (24.5%) children had adverse events that were thought by the investigator to be possibly related to the study medication (Table 4). The most frequent categories included gastrointestinal disorders (especially vomiting and diarrhea) and hematologic disorders (anemia and eosinophilia).

Only six patients (1.9%) had severe adverse events; two had anemia and one each had gastroenteritis, viral hepatitis, urticaria and malaria (recurrence on day 28). Only urticaria was considered to be drug related. The child with severe gastroenteritis developed gastroenteritis and died after hospital discharge, but this death was not considered to be related to study medication.

Hemoglobin levels decreased from baseline to day 3 and then increased to day 28, consistent with resolution of the malaria infection. Most of the hematologic criteria shifted toward normal from baseline by day 28, with the exception of neutrophil counts. Approximately half of the patients with normal neutrophil counts at baseline shifted to low counts. A total of 45/310 (14.5%) had neutrophil counts of $<10^9$/l at some point during the study. In most cases, the low counts were transient and occurred at day 0 or day 3, but 13 (4.2%) patients had isolated neutrophil counts of $<10^9$/l at day 28. Eight patients had neutrophil counts corresponding to NIH CTC grades 3 and 4. All grade 4 counts (one at baseline and two at day 28) had at least one subsequent count that was normal, as did three of grade 3 counts out of five patients. The remaining two patients with NIH CTC grade 3 neutrophil

Table 4 Adverse events (occurring after baseline but before recurrence in >2% of patients) suspected by the investigator to be related to study medication (safety population)

Adverse event	Bodyweight group			Total
	5—<10 kg	10—<15 kg	15—≤25 kg	
Patients: *n* (%)	154 (100)	110 (100)	46 (100)	310 (100)
Hematological				
Anemia	8 (5.2)	6 (5.5)	1 (2.2)	15 (4.8)
Eosinophilia	6 (3.9)	6 (5.5)	0 (0)	12 (3.9)
Gastrointestinal				
Vomiting	10 (6.5)	0 (0)	4 (8.7)	14 (4.5)
Diarrhea	5 (3.2)	5 (4.5)	1 (2.2)	11 (3.5)
Constipation	2 (1.3)	3 (2.7)	0 (0.0)	5 (1.6)
Nervous system disorders				
Clonus	7 (4.5)	5 (4.5)	1 (2.2)	13 (4.2)
Hyperreflexia	1 (0.6)	2 (1.8)	1 (2.2)	4 (1.3)
Skin/subcutaneous tissue disorders				
Rash	6 (3.9)	3 (2.7)	0 (0)	9 (2.9)

counts had no follow-up evaluations. The low neutrophil counts at days 0 and 3 (and in one case at day 28, where the patient had a new malaria infection) were probably malaria-related. Malaria is known to be associated with neutropenia, possibly due to splenic sequestration of neutrophils. The significance of the low neutrophil counts observed on day 28 is unclear, but, as with cases seen at day 0 or 3, there did not appear to be any clinical consequences, in terms of infections. Also, the observed neutrophil counts should be considered in the light of the reported lower counts in healthy Africans, particularly very young children, than in Caucasian patients (Lugada et al., 2004).

Electrocardiographic changes included a decrease in heart rate from baseline, with slight increases in PR, QRS and QT intervals. The QTc interval (corrected by Bazett's formula) showed slight, clinically non-significant increases (<30 msec in 211/273, 77.3% and >60 msec in 11/273, 4%), and mean and median values at day 3 remained within the normal range. One patient (0.4%) with normal QTc at baseline had a slightly prolonged QTc on day 3 (403 to 454 msec), and 19/273 patients (7.0%) were borderline. Two of three children with QTc prolongation at baseline reverted to normal by day 3. Children with borderline prolonged QTc at baseline remained borderline at day 3. No patient had a QTc interval >500 msec. Shift analysis (based on Fridericia's formula) showed no patient with QTc prolongation at baseline or day 3.

4. Discussion

The primary aim was to assess the safety of the six-dose co-artemether regimen in the treatment of falciparum malaria in children and infants weighing 5—25 kg, in order to allow a comparison with previous studies using four doses of co-artemether in pediatric patients weighing 5—25 kg (Hatz et al., 1998; Irion et al., 1997; Von Seidlein et al., 1997, 1998). The four-dose regimen appears sufficient to provide 28-day cure rates greater than 95% in regions where patients were partially immune and in areas without multidrug resistance (Lefèvre et al., 2001). However, higher dosages (e.g. six doses given over 3 days) are required to give similarly high cure rates in regions such as Southeast Asia, with drug-resistant *P. falciparum* strains, since the four-dose regimen gives suboptimal (<85%) cure rates under these circumstances (Lefèvre et al., 2001; Van Vugt et al., 1999).

In view of the concerns expressed by the WHO about the short- and long-term effectiveness and safety of the four-dose regimen of co-artemether, and their desire to have a single global dosing regimen for this medication, the underlying purpose of this study has been to determine whether or not the safety profile of the six-dose co-artemether regimen will permit it to replace the four-dose regimen. Studies in Southeast Asia have already shown that the six-dose co-artemether regimen is more effective than the four-dose regimen, while remaining equally safe and well tolerated (Lefèvre et al., 2001; Van Vugt et al., 1999). However, the six-dose regimen has not previously been studied in children weighing <10 kg.

An open-label, non-comparative design was adopted because no suitable comparator was available. In our study, co-artemether treatment demonstrated good efficacy, with corrected cure rates greater than 90% in all bodyweight groups, irrespective of the level of parasitemia and body temperature.

In the treatment of malaria, background immunity to the malarial parasite from repeated infections usually acts synergistically with antimalarial drugs to achieve better cure rates than in non-immune individuals, such as young children (Ezzet et al., 1998). In our study, the six-dose co-artemether regimen was equally effective in partially immune infants and those who were likely to be non-immune on the basis of their age and malaria history. The response to treatment was rapid in all groups, with a median time to fever clearance of less than eight hours (although some of the effect may have been attributable to acetaminophen). The median time to parasite clearance was approximately 30 hours. The rapid parasite clearance and the antigametocyte effects of the six-dose regimen are compatible with decreased risk of developing drug resistance.

Almost half the patients weighed 5—<10 kg and the treatment regimen was well tolerated. This was despite these patients receiving higher doses, on a mg/kg basis, than those in higher bodyweight groups. Most of the adverse events, which were mild, had been reported previously (Von Seidlein et al., 1998) and were indicative of symptoms of malaria or other infections common in this population. Only one patient had a serious adverse event (urticaria) considered to be related to the study medication. The patient was hospitalized and co-artemether treatment was withdrawn. The urticaria resolved after four days.

No significant abnormal laboratory values associated with co-artemether were recorded. Due to the chemical similarity between lumefantrine and the aryl-amino group of halofantrine (which is known to cause delayed ventricular repolarization manifested by QTc interval prolongation), the

possibility of a cardiotoxic effect of lumefantrine was investigated. These studies, both in vitro and in vivo, showed that lumefantrine lacked the cardiotoxicity of halofantrine (Bakshi et al., 2000; Bindschedler et al., 2000; Lefèvre et al., 2001; Van Vugt et al., 1999). No patient had a QTc interval >500 msec; the occasional increases of >60 msec occurred mostly in the youngest infants (aged <2 years). QTc changes were comparable with those reported with the four-dose regimen. The Committee for Proprietary Medicinal Products (1997) suggested that prolongation of a QTc increase of >60 msec raises concerns about the potential risk of arrhythmias, but the applicability of these adult values to small children with malaria is unknown. In high doses, artemether did not give rise to prolonged QTc intervals (Price et al., 1999). Moreover, significant prolongation of the QTc interval during treatment with other antimalarial drugs (chloroquine, sulfadoxine—pyrimethamine) was considered to be independent of treatment, but weakly correlated with baseline parasitemia and pyrexia (Von Seidlein et al., 1997). In view of the findings of these and earlier studies, it seems that the six-dose regimen of co-artemether is unlikely to be associated with cardiotoxicity. The WHO report of an informal consultation of international malaria experts on the use of anti-malarial drugs (WHO, 2000) concluded 'there is no evidence of increased toxicity with the 6-dose as compared to the 4-dose regimen of co-artemether in malarial areas'.

5. Conclusions

The six-dose regimen of co-artemether is a safe and well-tolerated treatment for acute falciparum malaria in African pediatric patients weighing 5—25 kg. Treatment results in rapid clearance of parasitemia and fever, gives high cure rates, and appears to be equally effective in non-immune and partially immune infants. The six-dose co-artemether regimen, therefore, fulfils the requirements of the WHO for an effective and safe therapy of falciparum malaria in infants and children who are most susceptible to develop malaria.

Conflicts of interest statement

This study was performed in collaboration with WHO and was partially funded by Novartis Pharma AG, Basel, Switzerland. Some of the authors are Novartis employees and have no conflicts of interest concerning the work reported in this paper.

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