Efficacy of Artemether-Lumefanthrine Combination in Rural Nigeria

Okoli Charles Ogbonna, PhD[1]

Mamah Cyril Chukwukama, MPharm[1]

Ubaka Chukwuemeka Michael, MPharm[2]*

Ezike Adaobi Chioma, PhD[1]

Akah Peter Achunike, PhD[1]

[1]*Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, Nigeria. Department of Clinical Pharmacy and Pharmacy Management, University of Nigeria, Nsukka, Nigeria.*

[2]**Ubaka Chukwuemeka Michael, MPharm Dept of Clinical Pharmacy and Pharmacy Management, University of Nigeria, 410001, Nsukka*

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ABSTRACT

Context/Objective: Irrational and inadequate drug use is common among rural natives of developing countries and this trend threatens the therapeutic life spans of currently recommended artemisinin combination drugs. This study tested the efficacy of artemether-lumefanthrine in children in rural dwellings of Nigeria.

Method: The 14-day 2003 WHO antimalarial efficacy protocol was used. Eighty children were recruited and a six-dose treatment of the drug administered. Non-PCR adjusted cure rates and treatment failures were the measured outcomes.

Results: Seventy six children completed the study as stipulated by the WHO protocol. Nearly all the children recovered clinically. About 94% (71/76) had similar fever clearance time of 3 days, with only one patient having mild fever on the 14th day. Early treatment failure was seen in four patients, late clinical failure was observed in one patient, but no report of late parasitogical failure was recorded. A non-PCR adjusted adequate clinical and parasitological response was therefore seen in 93% (71/76) of patients. The mean fever and parasitemia clearance was 48.5±25.2 and 39.3±20.1 respectively.

Conclusion: Artemether-Lumefanthrine combination is still an effective antimalarial option in rural Nigeria; however the absence of an absolute efficacy may be a sign of a failing efficacy profile.

INTRODUCTION

Malaria is still an endemic disease in Africa, with Africa accounting for over 70% of the world's prevalence (WHO, 2001; Snow et al, 2005). It still kills over one million people worldwide with over 90% of these people in Africa (Abuaku et al, 2005). Children in Africa are not spared with over 20% of childhood death attributed to malaria alone (WHO, 1999). With malaria affecting the poorest countries of the African regions (Gwatkin & Gulliot, 2000), inequity in distribution of malaria treatment and interventions also poses a great deal of problem (Uzochukwu et al, 2002). Efforts have

been made to make available cost-effective treatments such chloroquine and artesunate monotherapy to rural areas where any form of therapy is made available (Uzochukwu et al, 2002).

With failure rates ranging between 50 to 95% reported for chloroquine in parts of Nigeria (Falade et al, 2005; FMOH, 2004) and resistance to the classical antimalarial drugs, notably – chloroquine, sulfadoxine-pyrimethamine, mefloquine, quinine been well documented (White, 1992; Krogstad, 1996). Nigeria's Ministry of Health has endorsed the WHO recommendation of artemisinin-based combination therapy for the treatment of uncomplicated malaria. Artemether-lumefanthrine combination is the first choice in Nigeria's national antimalarial policy (FMOH, 2004). There has also been considerable interest in using multiple drugs with different mechanisms of action for treatment of malaria (WHO, 2001; White, 1999) and had led to the recommendation and use of ACTs and NACTS in nearly all parts of Africa (Sowunmi et al, 2007).

Artemether-Lumefanthrine is a fixed dose combination tablet containing artemether and lumefanthrine. The combination offers the rapid but short-lived schizonticidal effect of the former and prolonged antimalarial effect of lumefanthrine (Lefèver et al, 2001). It currently comes as a six dose regimen which was found to be more effective in multi-drug resistant areas than its earlier four dose regimen (van Vugt et al, 1998). Comparatively, artemether-lumefanthrine combination has been shown (by a meta analysis of 32 published efficacy studies) to be the most effective ACT and as good as any other combination in all geographical regions of the world (Jansen et al, 2007; Makanga and Krudsood, 2009). However, new findings have shown emerging failure to treatment with this combination ranging from 0 to 3.3% not necessarily from resistance but from reduced sensitivity on the lumefanthrine moiety (Ashley et al, 2008; Mizuno et al, 2009).

In most developing countries there have been claims of irrational and inappropriate use of medicines among health providers in rural settings. These claims are majorly fingered towards inadequate dosing of Artemether-Lumefanthrine, a "free" antimalarial in such settings, due to its low availability at the health care centers. This may lead (not entirely though) to emergence of therapeutic failure, numerous adverse effects and most importantly drug resistance. This basis informed the focus of this study, which was to assess the efficacy of artemether-lumefantrine in treatment of uncomplicated malaria among children of rural communities in Nigeria where irrational drug use is said to be at the highest.

METHOD

Study design

This was a randomized, prospective, open-label and non comparative study conducted between June and November 2009.

Study site

The study site was a rural hospital (Rural Comprehensive Health Center, Obukpa), an outpost of University of Nigeria Teaching Hospital (UNTH), Ituku/Ozalla, Enugu State, Nigeria. The centre was built to take care of the health needs of Obukpa rural community and the surrounding catchments areas which include Ovoko and Iheakpu-awka, all in Enugu State, Nigeria. The centre operates with the standard set by the parent hospital, UNTH. This part of the country is predisposed to heavy malaria attacks throughout the year (hyperendemic), especially during the wet seasons when this study was conducted.

Test protocol

A written ethical consideration was granted by the Medical Board of the Hospital. Sample size estimation was done by taking anticipated population proportion of clinical failures (P) of 0.25 (as suggested treatment failure range between 25-30%), a confidence interval of 95% and a precision (d) of 10%. An acceptable sample size of 72 patients was obtained but 80 patients were recruited to make up for any loss during follow up.

Patients (children aged between 3 months-12 years) were selected on the basis of the following criteria- detectable parasitemia (P. falciparum) levels (>1000 parasties/µl), axillary temperature levels above 37.50C or a history of fever a day or two before the study, no history of prior antimalarial drug use 2 weeks prior to the study and no other diagnosable co-existing illness.

The enrolled patients were clerked for their age, sex, weight and presenting complaints by the attending physician. The physician also examined the patients to rule out any confounding disease (such as respiratory tract infections, measles and abscesses) presenting with fever as with malaria. Patients' blood samples were collected and a rapid stain (10% Giemsa stain for 10 min) was done to screen patients for full enrollment. The second stain (2.5% Giemsa stain for 60 min) was done to measure the parasitemia levels (asexual parasites/µl) and this evaluation was done independently by two laboratory scientists.

Parents/caregivers of patients were formally informed of the study, its benefits and risks and oral consent to participate in the study and commitment to follow up was obtained in conformity with local and international guidelines on research (WHO, 2001b).

Patients were then given different doses of the artesunate-lumefantrine combination drug (Coartem®, Novatis, Switzerland) as described on the dug's official leaflet insert based on body weight measurements. The drugs (tablets were crushed and mixed with honey) were administered orally in the presence of a trained nurse and patients who vomited repeatedly were excluded from the study. Though 55 patients were hospitalized during the study, other patients, who refused hospitalization, were encouraged to come daily for 2 days for treatment. After the third day of treatment, caregivers were given a schedule for follow-up. They were also told to monitor symptoms of the children and to return immediately if fever or any other symptom worsened. On days 3, 7 and 14, the patients' blood were collected on slides, thin stained and parasitemia level quantified microscopically. Clinical response follow-up was done on alternate days and then on days 10 and 14. A fourteen day parasitemia and clinical response duration instead of the customary 28 days was done due to difficulty in establishing recrudescence or re-infection after fourteen days of treatment and the ease of patient loss during follow-up. Similar studies also employed this method[12, 13]. Hematological data were also assessed using hemoglobin count, erythrocyte sedimentation rate and leukocyte count. Side effects were also noted and taken as worsened or new events observed after treatment. Rescue treatments for severe malaria (quinine injection) and hyperthermia (antipyretics - paracetamol tablets) were provided.

Study outcomes

Outcome was measured by cure rate (adequate clinical and parasitological response-ACPR) which was defined as percentage of patients with absence of detectable parasites in blood smears after repeated counts on day 14 and no record of treatment failure in the study. Also fever clearance time was checked and defined as time (in hours) for body temperature to fall to or below 37.5oC after drug treatment. Improvements in other symptoms and hematological values were also noted. Treatment failures (early treatment failure, late clinical failure and late parasitological response) were also noted. Early treatment failure (ETF) was defined as any sign of severe malaria on any treatment day, parasitemia levels on day 2 higher than day 0 and persistent parasitemia on day 3 with fever. Late clinical failure (LCF) was defined as any sign of severe malaria on any day after day 3 and detectable parasitemia and fever on any day after treatment, without the patient having an early treatment failure. Late parasitological failure (LPF) was defined as detectable parasitemia and fever on day 14 without any early treatment failure or late clinical failure (WHO, 2003).

Data was analyzed as descriptive statistics using SPSS (version 13, Chicago IL)

Table 1. *Demographic characteristics of study participants and presenting complaints of caregivers in the efficacy study of Artemisinin-Lumefanthrine combination (Coartem®)*

Variable	*n (%)* [a]		
Gender			
Male/Female	48/32		
Age		**Weight, kg**	
Infancy (<1yr)	8 (10.00)	5-14	10 (12.5)
Pre-School/Nursery (>1yr - <5yr)	55 (68.75)*	15-24	49 (61.25)*
Primary School (>5 yr - 10yr)	17 (21.25)	25-34	21 (26.25)
Presenting complaints	**Day 1**	**Day 3**	**Day 14**
Fever	80 (100.00)	4 (5.00)	1¶
Headache	13 (16.25)	-	-
Loss of appetite	20 (25.00)	-	-
Weakness	8 (10.00)	12 (15.00)	2 (2.5)
Cough	27 (33.75)	-	-
Vomiting	23 (28.75)	-	1 (1.25)
Diarrhea	6 (7.50)	-	-
Chills	8 (10.00)	-	-
Rigor	12 (15.00)	-	-

*n represents frequency of occurrence and in percent; a patient could present with more than one symptom. Fever represents temperatures 37.5oC and above. ¶ shows fever on day 7. a shows that characteristics of patients enrolled but lost due to follow up were included. * shows statistical significance at P<0.05 (ANOVA, Students-t-test)*

and presented as frequencies or percentages for clinical and hematological data. Analysis of variance was run for differences in demographic characteristics (age and weight) of the children with P<0.05 considered statistically significant.

RESULTS

Patients

Eighty patients were successfully screened and enrolled for this study. Two patients were lost to follow-up on days 7 and 14 and could not be found or accounted for. Two patients also violated protocol by taking additional antimalarial treatments on days 7 and 10 (due to perceived ineffectiveness of test drug). No voluntary withdrawal was recorded. Therefore, only 76 (95%) patients successfully completed the 14-day study. Demographic characteristics of the recruited patients are displayed in Table 1. Majorities (60%) of the patients were males and more than two-third (68.7%) were aged < 5 years.

All the patients presented with fever on admission/screening, and about a third also presented with various symptoms ranging from cough (33%), vomiting (28%) and loss of appetite (25%). These findings are also shown in Table 1. On day 3, nearly all of the admitting complains had abated on completion of treatment except of weakness which was noticed in 15% of patients on day 3. However, only 2 of these patients complained of weakness after 14 days of follow-up. Other side effects observed were abdominal upsets in 5 children in the preschool age.

Outcomes

Parasitemia levels of patients who successfully completed the study are displayed in Table 2. On day 3, about 54% of the patients had a complete parasite clearance while 19 patients (25%) had parasite levels above 100 parasites/HPF with one patient still having high (1000 parasite/HPF) parasite levels. Four patients (5.26%) had detectable parasitemia and fever simultaneously

thus an ETF of 4. On day 7, 69 patients (90.7%) had no traceable parasites in their blood, but seven patients still had detectable parasitemia. However, out of these seven, only one patient who was different from the earlier 4 (early treatment failure), had both detectable parasitemia and elevated axillary temperature of 39.5^{0}C. Thus an LCF of 1 was obtained. On day 14 of the study, only 72 (94.7%) of the patients had their parasites in the blood successfully cleared, with 4 patients (5.3%) still having varying parasitemia in their blood. Since none of the latter patients developed any new fever episode, the LPF was 0. However, ACPR was found in 71 patients (representing 93.4% of the study population).

The overall mean ± standard deviation (SD) of parasitemia and fever clearance times for patients who had absolute clearance of parasites (72/76) and fever (75/76) before day 14, were 48.5 ± 25.2 hr and 39.3 ± 20.1 hr respectively.

DISCUSSION

This study presents the results of an efficacy study on the antimalarial effect of artemether-lumefanthrine combination in treatment of uncomplicated malaria in children living in rural Nigeria. The results showed that the combination is efficacious with an uncorrected ACPR of 93.4% and a near absolute resolution of all complaining symptoms. Studies conducted in Nigeria, which also assessed the efficacy of this drug combination among children, reported similar non-PCR adjusted efficacy rates of between 93.9 and 96.8% (Falade et al, 2008; Falade et al, 2008b). Similar results have also been produced in some other African studies (Syaril et al, 2008; Adjuik et al, 2002), but higher efficacy rates have been shown to occur when PCR-adjustments are done (van de Broek et al, 2006). With a 14-day adequate clinical and parasitological response of 93% for artemether-lumefanthrine, the result of this study is comparable to some studies with similar efficacy profile after PCR adjustments (Martesson, 2005; Mukthar, 2007). Studies on other artemisinin combination drugs in children, such as artemisinin-amodiaquine in other African countries using a similar parasitemia clearance rates on day 14 as the primary endpoint, showed 91% cure rate in Kenya; 93% in Senegal and 98% in Gabon (Ekanem et al, 1987).

A low early treatment failure ETF (5%) on day 2 with relief of parasitemia and fever is an indication of rapid action of this drug combination. However, delayed effect which is indicated by the late treatment and parasitological failures were evidently low with this combination in this study.

The onset of weakness in some patients may be attributed to the effect of drug on the patient as reported in a similar study (Okoli et al, 2010). These studies reported severe weakness in some of the patients used in various artemisinin combination efficacy studies. However, these side effects seemed to be age dependent, because the younger children (pre-school age group (age 1-5 years), were examined and reported to be weaker than the older children. Other side

Table 2. *Degree of parasitemia of patients in the efficacy study of Artemisinin-Lumefanthrine combination (Coartem®)*

Treatment day	Parasitemia level (asexual parasites/µl)				
	Nil	+	++	+++	++++
0	-	41 (53.94)	28 (36.82)	6 (7.89)	1 (1.31)
3	57 (75.00)	18 (23.68)	1 (1.31)	-	-
14	72 (94.74)	3 (3.94)	1 (1.31)	-	-

Values in parenthesis are percentages. Nil=indicates no parasite seen, +=1-10 parasites/100 High Power Field, ++=11-100 parasites, +++=>100≤1000 parasites/100 High Power Field, >1000 parasites/ 100 High Power Field.

effects reported in other studies like medication-induced emesis were observed in only one patient in this study (Oyakhirome et al, 2007; Sowumni et al, 2005; Falade, 2008). However, artemisinin derivatives are generally safe when used in treatment of malaria (Looareeesuman et al, 1992; Nosten et al, 1994). There was no record of discontinuation or withdrawal of medication from any patient.

The limitations of this study are peculiar to other studies in similar settings (Meremikwu et al, 2006; Adjei et al, 2008). The use of the 14-day follow up instead of the 28-day follow up was due to difficulty in reaching patients and ensuring patient participation after such long periods. It is however in compliance with the recent WHO recommendation in assessing clinical efficacy of antimalarial drugs which proposed a 14-day study period in high areas of transmission and where genotyping may not be feasible (WHO, 2003). With the high efficacy reported for this combination in this study, a 28-day PCR adjusted efficacy may not always produce high rates but may prove to be much lower as shown in some other studies employing also the 14-day efficacy (Grandesso, 2006; Ndayiragiye, 2004). However, the non-use of the 28 days made the observation of recrudescence, an indication of treatment failure, rather difficult.

CONCLUSION

The artemether-lumefanthrine combination has high clinical efficacy for the treatment of uncomplicated malaria in children in the rural community of Iheakpu-Awka, Enugu, Nigeria. Even with the early treatment failures observed, adherence to recommended dosing will help to preserve the therapeutic life of this common and "free" artemisinin combination drug.

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CONFLICT OF INTEREST

The authors also declare there is no conflict of interest.

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