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Evaluation of the Comparative Efficacy and Safety of Artemether-Lumefantrine, Artesunate-Amodiaquine and Artesunate-Amodiaquine-Chlorpheniramine (Artemoclo™) for the Treatment of Acute Uncomplicated Malaria in Nigerian Children

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Key Words
Childhood malaria · Artesunate · Amodiaquine · Artemether · Lumefantrine · Chlorpheniramine

Abstract
Objective: To evaluate the comparative efficacy and safety of artemether-lumefantrine (AL), artesunate-amodiaquine (ASAQ) and artesunate-amodiaquine-chlorpheniramine (AQC) for the treatment of acute uncomplicated malaria among Southwest Nigerian children. ***Subjects and Methods:*** One hundred and sixty children aged 6 months to 14 years with acute uncomplicated malaria were randomized to AL (n = 53), ASAQ (n = 53), or AQC (n = 54). Enrollees were seen daily on days 0–3 and then on days 7, 14, 21, 28 and 42 for clinical and parasitological evaluations. Paired samples of genomic DNA at enrolment and at the time of recurrent parasitaemia were genotyped using nested PCR to distinguish between reinfection and recrudescence. Detailed haematological and biochemical evaluations were carried out in a subset of enrollees on days 0, 7 and 28 as part of a safety evaluation. ***Results:*** Of the 160 children, 144 (90%) completed the study. The mean fever clearance times and parasite clearance times for AL, ASAQ and AQC were comparable (p = 0.94 and p = 0.122, respectively). On day 14, the adequate clinical and parasitological response (ACPR) for AL and AQC was 100% and for ASAQ it was 90% (p = 0.39). The PCR-uncorrected results on days 28 and 42 and the ACPR-corrected results on day 42 were similar for all drugs (p = 0.62 and p = 0.56, respectively). AQC resulted in the best parasite clearance and haematological recovery on day 2 (p = 0.022 and p = 0.018, respectively). Biochemical parameters were not adversely affected by the three artemisinin-based combination therapies (ACTs) and these were well tolerated. ***Conclusion:*** The three ACTs were efficacious and safe, but AQC resulted in a better haematological recovery on day 2 and higher cure rates throughout the study period.

Introduction

Artemisinin-based combination therapy (ACT), which was first recommended by the World Health Organization (WHO) in 2001, has become widely accepted as the best option for the treatment of acute uncompli-

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cated falciparum malaria [1]. ACTs have been widely accepted because of their efficacy against falciparum infections of varying sensitivities [2–5]. The rapid schizonticidal effect of artemisinin derivatives, combined with the schizonticidal effect of another efficacious longer-acting anti-malarial drug with a different mechanism of action, forms the basis for the sustained efficacy of ACTs. However, companion drugs for ACTs are few and limited. Amodiaquine in combination with artesunate is one of the preferred ACTs recommended by the WHO and has been adopted as the drug of choice for the treatment of acute uncomplicated falciparum malaria in some countries [3]. Lumefantrine, mefloquine, piperaquine and sulfadoxine-pyrimethamine are other recommended companion drugs in ACT [3].

Amodiaquine in combination with chlorpheniramine has been reported to be significantly more effective than amodiaquine alone for the treatment of acute uncomplicated falciparum malaria [6, 7]. This is most probably due to the enhancement of the anti-malarial effect of amodiaquine by chlorpheniramine. The combination of amodiaquine-chlorpheniramine could be a better alternative to amodiaquine alone as a companion drug in ACT as chlorpheniramine would act as a resistance modulator should there be mild amodiaquine resistance.

Nigeria adopted ACT as the therapeutic regimen of choice for the treatment of acute uncomplicated falciparum malaria, with artemether-lumefantrine (AL) and artesunate-amodiaquine (ASAQ) as the preferred options, in 2005 [8]. Artemoclo™ is a new fixed-dose formulation of artesunate-amodiaquine plus chlorpheniramine. Chlorpheniramine has been added to artesunate plus amodiaquine in Artemoclo as a resistance modulator to enhance the efficacy of amodiaquine as resistance could limit the efficacy of amodiaquine. In this report, we present the findings of a study which evaluated the comparative efficacy and safety of AL, ASAQ and artesunate-amodiaquine-chlorpheniramine (AQC) for the treatment of acute uncomplicated falciparum malaria.

Subjects and Methods

Study Location

The study reported here is the Ibadan part of a multi-centre study designed to assess the comparative efficacy and safety of AL, ASAQ and AQC for the treatment of acute uncomplicated malaria in 4 of 6 geopolitical zones in Nigeria, i.e. southwest (Ibadan), north-central (Ilorin), northwest (Kaduna) and southeast (Enugu). The Ibadan study was conducted at the General Outpatient Department of the University College Hospital (UCH), Ibadan, and the Primary Health Care Center (PHC), Idi-Ayunre, Oluyole Local Government Area. The Idi-Ayunre PHC is located 20 km from the city of Ibadan and serves 5–6 villages around it. Both the UCH and the Idi-Ayunre PHC are located in the rain forest belt of Southwest Nigeria. Malaria transmission is perennial in the study area, with peak transmission occurring during the months of the rainy season (May to October) and a nadir in the months of the dry season (November to April). Enrolment into this study was extended to the rural PHC because, unlike in the past, it was difficult to find patients who satisfied the enrolment criteria fast enough at the UCH centre. One hundred and sixty subjects were enrolled into this study.

Ethical Issues

This study was conducted according to Good Clinical Practice and the Declaration of Helsinki. The University of Ibadan/UCH Institutional Review Committee approved this study. Written or witnessed verbal informed consent was obtained from the parent or guardian of each child.

Study Design

The study design was an open-labelled comparison of AL, ASAQ and AQC. Inclusion criteria were: children aged 1–14 years of either sex with microscopically confirmed *Plasmodium falciparum* malaria, asexual parasite density ≥1,000/μl, axillary temperature ≥37.5°C or a history of fever in the preceding 48 h, symptoms compatible with acute uncomplicated malaria and provision of signed informed consent by the parent or guardian. Exclusion criteria were: children with signs of severe malaria such as impaired consciousness, multiple convulsions or coma [3], concomitant illness or malnutrition, other causes of fever, severe anaemia (haematocrit <15%), a history of hypersensitivity to any of the study drugs and a history of anti-malarial drug use, except for chloroquine or sulfadoxine-pyrimethamine, in the 7 days preceding study.

A power calculation with an α level of significance at 5% showed a minimum sample size of 143, but 160 subjects were enrolled into this study. The enrolled children were randomly allocated to one of three groups to receive one of the three ACTs according to a pre-generated randomization table. A randomization table was generated in blocks of 10 using a table of random numbers. The study participants were allocated to the respective drug groups by the study nurse who was also responsible for administering the drugs under supervision at the clinic. The subjects were enrolled from August 2007 to May 2008. Fifty-three subjects, respectively, were randomized to receive AL and ASAQ while 54 received AQC. A research assistant administered the second daily dose of AL at home. Physicians and microscopists who were responsible for patient follow-up and slide examination were, however, blinded to the individual patient treatment group allocation. Children who developed serious adverse events, suffered recurrent vomiting after redosing or violated the protocol or whose parent/guardian retracted consent were withdrawn from the study.

Children treated with AL received a 6-dose regimen of AL (Coartem™; Novatis Pharma) at a standard weight-based dosage as follows: 5 to <15 kg, 1 tablet twice daily for 3 days; 15 to <25 kg: 2 tablets twice daily for 3 days, and 25 to <35 kg: 3 tablets twice daily for 3 days. Children in the ASAQ group received artesunate – 4 mg/kg to the nearest next quarter of a tablet – plus amodiaquine (Camoquine; Pfizer Ltd.) at a dose of 10 mg/kg, while children in the AQC group received a fixed-dose formulation of

AQC in the form of Artemoclo manufactured by Neimeth Pharmaceuticals under good manufacturing practices. Each tablet of AQC contains 100 mg artesunate, 300 mg amodiaquine and 4 mg chlorpheniramine. The amodiaquine component was used as the reference for dosing at a dose of 10 mg/kg to the nearest next quarter of a tablet.

Pre-Treatment

A thorough medical history, a physical examination including vital signs, a specific neurological examination and baseline signs and symptoms of malaria for a safety evaluation of treatment-emergent signs and symptoms were carried out. Blood samples for definitive parasite counts and haematocrit evaluations were done at every visit. Pre-treatment blood spots for PCR evaluation were also prepared from each enrollee for subsequent genotyping of malaria parasites in case of a recurrence of parasitaemia after the initial clearance. Venous blood was obtained from a subset of study volunteers for detailed haematological and biochemical evaluations. The haematological evaluation included haematocrit, haemoglobin, red blood cell counts and white blood cell counts with differential and platelet counts. Blood chemistry parameters included bilirubin, creatinine, alanine transaminase and aspartate transaminase. All parameters were recorded in a case record form specifically provided for this purpose.

Study Drug Administration

Older children swallowed the study drug whole with water, while younger children less than 4 years of age received the drug crushed and mixed with water. Parents and guardians were asked to feed children who received AL a fat-containing meal soon after dosing to enhance absorption. The children were observed for 1 h to ensure that the study drug was not vomited. Any patient who vomited the study drug within 1 h received the same dose of the drug again and was observed for vomiting as with the initial dosing.

Patient Follow-Up

Patients were seen daily on an outpatient basis from day 0 to day 3 and then on days 7, 14, 21 and 28. Parents were encouraged to bring their children in for follow-up on day 42. The axillary temperature, pulse rate and treatment-emergent signs and symptoms were evaluated and a blood film for malaria parasite evaluation was carried out at each follow-up visit in the clinic or at home for those who missed the follow-up appointment. Parents/guardians were also encouraged to bring their children to the clinic whenever there was a need for medical attention even if this was outside of their appointment days. The therapeutic response was assessed using clinical and parasitological parameters. Blood spots were blotted on Whatman™ filter paper for PCR at the recurrence of parasitaemia for the genotyping of isolates to distinguish between recrudescence and reinfection. In addition, haematology and blood chemistry evaluations were repeated on days 7 and 28 for patients randomized to detailed haematology and blood chemistry evaluations. Giemsa-stained blood films prepared from a finger prick at each visit were examined under an oil immersion objective at ×1,000 magnification for parasite detection, quantification and morphology. The parasite density was estimated in thick films by counting the number of asexual parasites relative to about 200 leucocytes. The definitive parasite density was calculated using an assumed white blood cell count of 8,000/mm^3.

Efficacy Evaluation

Study outcomes were classified as early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF) or adequate clinical and parasitological response (ACPR) [9]. ETF was defined as the development of danger signs of malaria or severe malaria on post-treatment day 1, 2 or 3 in the presence of parasitaemia, parasitaemia on day 2 higher than the day 0 count irrespective of the axillary temperature, parasitaemia on day three ≥25% of the count on day 0 and parasitaemia on day 3 with an axillary temperature ≥37.5°C. LCF was defined as the development of danger signs or severe malaria after day 3 in the presence of parasitaemia without previously meeting any of the criteria for ETF and presence of parasitaemia and an axillary temperature ≥37.5°C on any day from day 4 to day 28 without previously meeting any of the criteria of ETF. LPF, on the other hand, was defined as the presence of parasitaemia on any day from day 7 to day 28 and an axillary temperature <37.5°C without previously meeting any of the criteria for ETF or LCF. ACPR was defined as the absence of parasitaemia on day 28 irrespective of the axillary temperature without previously meeting any of the criteria for ETF, LCF or LPF. The cure rates on days 14, 28 and 42 were defined as the proportion of patients cleared of asexual parasitaemia within the specific time interval of the initiation of treatment with the respective study drug without recrudescence within the specified days. In addition to the cure rates, the mean fever clearance time (FCT), the mean parasite clearance time (PCT) and the proportion of patients cleared of patent parasitaemia at 24, 48 and 72 h following treatment were determined. The PCT was defined as the time elapsing from drug administration and the clearance of patent parasitaemia, while the FCT was defined as the time from drug administration until the axillary temperature fell below 37°C and remained so for at least 48 h.

Retreatment of Drug Treatment Failures

All patients in whom parasitaemia recurred following ASAQ or AQC treatment were retreated with AL, while those who had a reappearance of parasitaemia following AL treatment received ASAQ.

Safety Evaluation

The safety assessment consisted of monitoring and recording all adverse events whether volunteered, discovered via questioning or detected by physical examination. Also included were clinically significant changes in the values of haematology and blood chemistry parameters.

Molecular Genotyping

Genomic DNA was extracted from filter paper blood spots via the Chelex-100 method in a 96-well plate format as previously described [10]. Paired samples from every patient at enrolment and at the time of recurrence of parasitaemia were genotyped using a nested PCR amplification of the polymorphic regions of *P. falciparum* genes *msp1* (K1, MAD20 and RO33) and *msp2* (IC1 and FC27) as described elsewhere [11]. Samples (10 μl) of the nested PCR products were resolved on 2–2.5% agarose gels (Sigma-Aldrich) in 1× Tris-borate-EDTA buffer, stained with ethidium bromide and visualized via UV transillumination. If no alleles matched at any of the two genetic loci between day 0 and the day of recurrence, the infection was classified as a reinfection. If any allele was identical at any of the loci, the infection was classified as a recrudescence.

Table 1. Presenting complaints of children suffering from acute uncomplicated malaria treated with AL, ASAQ or AQC in Nigeria

Presenting complaints	Treatment group, n (%)			Total, n (%)	p value
	AL	ASAQ	AQC		
Fever	53 (100)	53 (100)	54 (100)	160 (100)	–
Anorexia	24 (46.2)	29 (54.7)	32 (59.3)	85 (53.5)	0.391
Vomiting	28 (52.8)	28 (52.8)	26 (48.1)	82 (51.3)	0.692
Headache	15 (28.8)	27 (52.9)	28 (51.9)	70 (44.3)	0.023
Chills and rigors	21 (41.2)	23 (43.4)	25 (46.3)	69 (43.7)	0.869
Cough	19 (35.9)	18 (35)	21 (38.9)	58 (36.3)	0.701
Abdominal pain	11 (21.2)	18 (34.0)	12 (22.2)	41 (25.8)	0.247
Diarrhoea	9 (17.3)	9 (17.3)	7 (13.0)	25 (15.8)	0.777
Irritability	6 (11.5)	7 (13.7)	12 (9.3)	18 (11.5)	0.773

Table 2. Baseline characteristics of children suffering from acute uncomplicated malaria treated with AL, ASAQ or AQC in Nigeria

	AL	ASAQ	AQC	p value
Total, n	53	53	54	
Sex[a]				
Male	28 (52.8)	30 (56.6)	25 (46.3)	0.56[b]
Female	25 (47.2)	23 (43.4)	29 (53.7)	
Age, months				
Mean ± SD	49.28±35.4	51.03±32.77	52.08±33.45	0.91[c]
Range	6–144	7–126	7–168	
Weight, kg				
Mean ± SD	14.38±5.74	14.78±5.46	14.69±5.82	0.93[c]
Range	5–35	5–30	5–25	
Temperature, °C				
Mean ± SD	37.68±1.17	37.74±1.06	37.41±1.18	0.51[c]
Range	35.5–40.7	36.0–39.8	38.5–40.2	
Parasite density, n/μl				
Geometric mean	13,524	15,817	16,183	0.76[c]
Range	1,115–244,157	1,000–230,793	1,109–151,259	
Haematocrit, %				
Mean ± SD	30.4±4.54	29.94±6.48	30.70±3.79	0.74[c]
Range	15–37	15–40	20–38	

[a] n (%). [b] χ^2 test. [c] One-way ANOVA.

Data Analysis

All generated data were entered into the computer and analysed using Statistical Package for Social Sciences version 15.0 software (SPSS Inc., Chicago, Ill., USA). The cure rates at the different time points were calculated as percentages. Efficacy analysis of the data was done for the intention-to-treat (ITT) and per-protocol (PP) populations. All of the children enrolled into the study were considered the ITT population. Patients who completed the study without violating the study protocol were considered the PP population. The effect size and OR with 95% CI were used to measure the treatment effect for the main outcomes. The means ± SD of normally distributed data were compared using Student's t test and ANOVA. Proportions were compared using χ^2 test. The results of haematology and liver enzymes over time were analysed using a paired t test comparing days 0 and 7 as well as days 0 and 28. Numerical values are given as means ± SD, and $p < 0.05$ was considered statistically significant.

Results

Patient Disposition and Demographic Data

The characteristics of the study participants in the three groups were comparable at entry. The details of the presenting symptoms of the study population are shown in table 1. The details of the baseline characteristics of the study patients at enrolment are shown in table 2. The 4 most common presenting complaints were: fever, n = 160 (100%); anorexia, n = 85 (53.5%); vomiting, n = 82 (51.3%), and headache, n = 70 (44.3%). The study drugs were well tolerated. Three of 53 (5.7%), 4 of 53 (7.6%) and 4 of 54 (7.4%) children treated with AL, ASAQ and AQC, respectively, vomited the study drug within 30 min of

Table 3. Treatment outcomes in Nigerian children suffering from acute uncomplicated malaria treated with AL, ASAQ or AQC

Characteristic	AL	ASAQ	AQC	p value
PP population (day 14)				
ACPR	45/45 (100)	49/50 (98)	49/49 (100)	0.388
LPF	–	1 (2)	–	
ACPR (PCR uncorrected; day 28)	41/45 (91.1)	46/50 (92)	47/49 (95.9)	
LPF	2 (4.4)	2 (4)	2 (4.1)	0.622
LCF	2 (4.4)	2 (4)	–	
PCR-corrected cure rate	43/45 (95.6)	46/48 (95.8)	47/49 (95.9)	
ACPR (PCR uncorrected; day 42)	28/38 (73.7)	32/40 (80.0)	32/37 (86.5)	
LPF/LCF	10/38 (26.3)	8/40 (20.0)	5/37 (15.5)	0.555
PCR-corrected cure rate	32/38 (84.2)	34/37 (91.9)	35/37 (94.6)	
ITT population	53 (100)	53 (100)	54 (100)	
LPF (day 14)	7/53 (13.2)	4 (7.4)	4 (7.4)	0.504
ACPR	46 (86.7)	49 (92.5)	50 (92.6)	
LPF (day 28)	9 (17.6)	5 (9.4)	7 (13.0)	
LCF	3 (5.7)	2 (3.8)	0 (0)	0.307
ACPR	41 (77.4)	46 (86.8)	47 (87.0)	
Mean FCT ± SD (range), days	1.21±0.51 (1–3)	1.19±0.48 (1–3)	1.16±0.38 (1–2)	0.94
Mean PCT ± SD (range), days	2.1±0.77 (1–4)	1.82±0.66 (1–3)	1.85±0.57 (1–3)	0.122
Presence of parasitaemia				
Day 1	37/51 (72.5)	36/51 (70.6)	36/52 (69.2)	0.944
Day 2	14/51 (27.5)	7/49 (14.3)	3/49 (6.1)	0.022
Day 3	1/49 (2.04)	0%	0%	0.335
Presence of fever				
Day 1	3/50 (6.0)	2/51 (3.8)	4/51 (7.8)	0.675
Day 2	3/50 (6.0)	1/50 (2.0)	2/51 (3.9)	0.545
Day 3	0 (0)	0/52 (0)	0/52 (0)	–
Mean haematocrit ± SD, %				
Day 2	29.2±4.9	27.2±4.4	30.0±4.8	0.018
Day 14	32.3±3.2	32.5±4.2	33.0±3.2	0.803
Day 28	35±4.0	35.1±3.2	34.7±3.0	0.787
Drowsiness				
Day 1	5/52 (9.6)	6/53 (11.3)	35/53 (66.6)	<0.0001
Day 2	1/51 (1.96)	5/53 (9.4)	18/53 (34.0)	<0.0001
Day 3	2/51 (3.9)	2/53 (3.6)	4/53 (5.1)	0.608

Values are presented as n (%) unless indicated otherwise.

drug administration. In no patient was there a recurrence of vomiting after redosing and no patient was withdrawn as a result of recurrent vomiting. Of the 150 enrollees, 16 (10.7%) did not complete the study. Of these 16, six (AL: n = 2; ASAQ: n = 3; AQC: n = 1) were lost to follow-up while 10 (AL: n = 6; AQC: n = 4) were withdrawn for various reasons. Reasons for withdrawal included protocol violations (AL: n = 3; AQC: n = 3), while 3 children (AL: n = 2; AQC: n = 1) were withdrawn because their parents retracted the consent they had provided earlier. The list of protocol violations included the administration of other anti-malarial drugs (n = 4) and a definitive parasite count below the cutoff value (n = 2). Two parents refused finger pricks for their children after day 3 when the children were fully recovered, while 1 parent travelled out of the study area and informed the study team. One child who was treated with AL was withdrawn because of a serious adverse event. The child convulsed at home about 18 h after enrolment. She had received 2 doses of AL before the seizure. She was taken to a private clinic in the community where she received intra-muscular and oral chloroquine and an anti-pyretic analgesic. She was free of patent parasitaemia by the end of day 2 when she was visited at home. She made an uneventful recovery

Table 4. Blood chemistry and liver enzymes among children with acute uncomplicated malaria treated with AL, ASAQ or AQC

Blood chemistry parameters/LFT	Day 0	Day 7	t value	p value	Day 28	t value	p value
AL							
Creatinine	0.878±0.72	0.850±0.310	0.868	0.449	0.767±0.197	0.997	0.392
Bilirubin	0.444±0.17	0.5±0.080	–2.330	0.102	0.533±0.28	0.974	0.402
AST	11.0±6.0	15.75±2.500	–9.127	0.003	12.33±5.85	–1.830	0.165
ALT	6.0±4.183	6.250±3.304	–2.143	0.122	8.167±5.811	–2.140	0.125
ASAQ							
Creatinine	0.800±0.6	0.980±0.669	–0.670	0.705	1.264±0.996	0.371	0.740
Bilirubin	0.467±0.25	0.650±0.240	1.000	0.156	0.436±0.163	1.000	0.423
AST	20.56±10.38	20.0±12.460	2.000	0.295	20.0±12.46	2.000	0.295
ALT	10.556±5.341	10.556±6.557	0.670	0.958	10.500±6.557	0.670	0.958
AQC							
Creatinine	1.036±0.693	0.533±0.250	2.355	0.100	0.657±0.230	0.670	0.670
Bilirubin	0.655±284	0.583±0.983	0.974	0.328	0.500±0.173	0.389	0.717
AST	12.82±6.06	14.83±5.9	3.000	0.659	13.430±8.460	0.551	0.551
ALT	14.364±10.327	17.333±5.317	1.640	0.200	11.00±6.590	0.000	1.00

Values are presented as means ± SD. AST = Aspartate amino transaminase; ALT = alanine amino transaminase.

and was followed up to day 28 for a safety evaluation. The 6 children who were lost to follow-up and the 3 whose parents withdrew consent fully recovered and were free of patent parasitaemia when they were seen last.

Outcome of Efficacy Evaluation

Of the 160 children who constituted the ITT population, 144 (90%), i.e. AL, n = 45 (84.9%); ASAQ, n = 50 (94.3%), and AQC, n = 49, completed the study as stipulated by the protocol (PP population). There was no record of ETF during the study. The mean fever and PCT for AL, ASAQ and AQC were similar. The proportion of children who were cleared of patent parasitaemia on day 2 (AL, 72.5%; ASAQ, 85.7%; AQC, 93.9%) was significantly higher (p = 0.022) (table 3) among those treated with AQC compared to AL and ASAQ. However, there was no significant difference in haematological recovery on days 14 and 28. All but 1 child who received AL were free of patent parasitaemia by day 3. The day 14 cure rate for AL and AQC was 100% while that for ASAQ was 49/50 (98%). The ACPR (PCR uncorrected) day 28 values were 91.1% (41/45) for AL, 92% (46/50) for ASAQ and 95.9% (47/49) for AQC. The PCR-adjusted cure rates for AL, ASAQ and AQC on day 28 were 95.6, 95.8 and 95.9%, respectively, while the figures for day 42 were 84.2, 91.9 and 94.6% for AL, ASAQ and AQC, respectively. The higher ACPR of AQC on days 28 and 42 were not statistically significant. When compared with AL at day 28, the cure rate for ASAQ had an OR of 1.119 (95% CI 0.214–5.347; p = 0.394) while that of AQC had an OR of 1.679 (95% CI 0.267–10.537; p = 0.581). The day 42 values for ASAQ were: OR 1.292, 95% CI 0.437–3.817 and p = 0.643; those for AQC were: OR 1.133, 95% CI 0.638–7.134 and p = 0.219. Further details of the results of the efficacy evaluation are shown in table 3.

Outcome of the Safety Evaluation

Most of the recorded adverse events were signs and symptoms of malaria, thereby making their assessment difficult. Adverse events recorded among the study participants (ITT population) were: fever, anorexia, vomiting, abdominal pain, cough and drowsiness. Those who received AQC were significantly more drowsy on days 1 (p < 0.0001) and 2 (p < 0.0001) (table 3). No study participant was withdrawn as a result of recurrent vomiting. The serum bilirubin was significantly higher on day 7 compared to day 0 among children who received AL (p = 0.003). The other paired tests conducted on blood chemistry and liver enzymes were not statistically different (table 4). Evidence of intra-vascular haemolysis was not detected in any of the participants. The haematological recovery was good in the three treatment arms. There was an early superior statistically significant (p = 0.018) haematological recovery among children who were treated with AQC compared to ASAQ and AL (table 3). One case of an observed serious adverse event which occurred during the study was not considered drug related.

Discussion

It is generally accepted that ACTs are the treatment of choice for acute uncomplicated malaria [2–5, 12]. The three ACTs had similar efficacies but AQC was better than AL and ASAQ. The response to treatment was prompt in the three treatment arms without any record of ETF. In addition to high cure rates, most of the other parameters for assessing efficacy such as PCT and FCT were also comparable among children randomized to all three study drugs (table 3). It is, however, noteworthy that the FCT and PCT in the present study were inaccurate measures because body temperature and parasite density were measured every 24 h from day 0 to day 3 and not every 6 or 8 h as in some other published studies [2]. The overall health of the children in this study was good.

A significantly higher proportion of children treated with AQC had parasitaemia clearance on day 2 compared to those who received AL and ASAQ. The haematological recovery was also significantly better on day 2 among children treated with AQC. The significantly better haematological recovery on day 2 was most likely a confirmation of the higher proportion of children cleared of patent parasitaemia on day 2. The full significance of this finding is still not clear. It could, however, be an indication of the enhancement of the anti-malarial effect of artesunate plus amodiaquine by chlorpheniramine. The failure to detect a statistically significant superiority in the cure rates of AQC over the others was probably related to the generally high efficacy of the three ACTs. The day 28 cure rates of 91.1, 92 and 95.9% for AL, ASAQ and AQC, respectively, are consistent with the high cure rates in previous reports of ACT efficacy [4, 5, 12–16]. The new combination of AQC, which is being evaluated for the first time, yielded the highest though not the most clinically significant cure rate of the three study drugs at all evaluated time points. AQC also yielded significantly higher PCR-corrected cure rates than AL on day 42. This is not surprising because amodiaquine, the companion drug to artesunate, in these combinations has a longer half-life than lumefantrine (the companion drug to AL), thus providing a longer post-treatment prophylaxis. As a corollary, the shorter post-treatment prophylaxis by AL may also be responsible for its relatively low day 42 cure rate. Many of the parasite recurrences on day 42 may actually have been reinfections which were misclassified as is often the case in areas where malaria transmission is intense [17].

Reported adverse events included fever, cough, vomiting and increased sleepiness. More children who received AQC were reported to have slept for significantly longer periods during the first 2 days of treatment than they usually did, and this could have been due to drowsiness, a well-known pharmacological effect of chlorpheniramine. This could also be beneficial for the recovery of the sick child. Drowsiness associated with AQC could, however, have adverse consequences for children while in school.

Conclusion

This study confirmed the efficacy of ACTs for the treatment of acute uncomplicated malaria even in an area of established drug-resistant infection such as Nigeria. The fixed-dose combination of AQC could be another addition to the currently available artemisinin combinations for the treatment of acute uncomplicated malaria, but evaluations with larger sample sizes are needed.

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