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Efficacy and safety of Artesunate +Mefloquine (Artequin®) in the Treatment of Uncomplicated *Falciparum malaria* in Ijede Community, Ikorodu LGA, Lagos State, Nigeria

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Artequin®, a combination of Artesunate and Mefloquine has been reported to be effective against multidrug-resistant *Plasmodium falciparum* malaria in other countries but not in Nigeria. We have now evaluated the efficacy and safety of this drug in the treatment of malaria in a high malaria transmission area. The WHO protocol was followed and the Health Centre of the Community was used. Out-patients having amongst other criteria, a pre-treatment parasite density of $\geq$1000 μL^{-1} of blood were enrolled for the study. Informed Consent was obtained and the drugs were given on days 0, 1 and 2. Each patient was followed up to day 28. Results showed that of the 1453 patients screened, 120 met the enrolment criteria but 115 (58 adults and 57 children) completed the trial. The success rates in adults on D1, D2, D3, D7, D14 and D28 were 53.4, 94.8, 100, 100, 100 and 98.3%, respectively. The success rates in children were 22.8, 98.25, 100, 100, 100 and 93.0%, respectively. Parasite clearance times in adults and children were 36.4 and 42.9 h, respectively. The mean fever clearance times were 11.75 and 12.25 h, respectively. Artequin® exhibited marked antigametocyte activity, with a gametocyte clearance time of 51.0 h. There were no major adverse reactions. The values of haematological and clinical indices of safety were within normal ranges. We conclude that Artequin® is efficacious, safe and well tolerated. Its use in the treatment of malaria is therefore recommended.

Key words: Artequin®, *Plasmodium falciparum*, malaria, ACTs

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INTRODUCTION

Malaria remains one of the greatest causes of morbidity in the world. Global estimates show that there are about 300-500 million cases of clinical malaria every year, with 85% of these from Africa (Teklehaimanot and Bostman, 1998). Currently 1.5 to 2.7 million deaths are attributable to malaria annually, 90% of them in Africa (Teklehaimanot and Bostman, 1998) In Nigeria, malaria is holoendemic and the risk of getting malaria is present all the time. It is the most common cause of outpatient hospital attendance in all age-groups and in all parts of Nigeria (Salako, 1997). Retrospective studies at Ijede Health Centre (courtesy of Dr. R.A.S. Mustapha, CMD, 2005) indicates that 80 to 85% of outpatient attendance in all age groups in that area is caused by malaria. Children 6 months to five years and to a lesser extent 5-11 years are prone to severe illness which, if untreated, often leads to death. Many adults in this high transmission area of Ijede are not spared.

The Drug Therapeutic Efficacy Test (DTET) Conducted on Chloroquine (CQ) and Sulphadoxine Pyrimethamine (SP) in 2002 showed a national average of Adequate Clinical and Parasitological Response (ACPR) of 39.2% (range 3.7 to 77.3%) and 56.7% (range 8.5 to 94.2%), respectively (Federal Ministry of Health, 2004). This was too poor.

The global malaria control strategy (Salako and Aderounmu, 1987) advocates prompt and adequate treatment as an essential measure to reduce the morbidity and mortality arising from the disease. However, there is great concern on the increasing reports of resistance to the first-line and the second-line drugs namely, CQ and SP, respectively (Ekanem *et al*., 1990; White, 1999). To overcome this problem, both the World Health Organization (WHO) and the Federal Ministry of Health advocated a change to artemisinin-based combination drugs which have been found to be effective in other countries. The principle advanced is that the probability of resistance developing simultaneously to two drugs with independent mechanisms of action is extremely low (White, 1999; White *et al*., 1999).

The Artemisinins are new drugs developed from the Chinese Warmwood (*Artemisia annua*) and the derivatives, namely, artemether, artesunate and dihydroartemisinin have now gained popularity as short acting drugs which could be used in combination with drugs which have long half-life (White and Olliaro, 1998; Okoye *et al*., 1997). The National Drug Therapeutic Efficacy Tests (DTET) conducted on two such combinations artesunate+amodiaquine and artemether+ lumefantrine in 2004 showed a national average of Adequate Clinical and Parsitological Response (ACPR) of 94.6 and 96.8%, respectively (Federal Ministry of Health, 2004). The National Policy on malaria treatment then recommended the use of Artemisinin-based Combination Therapy (ACTs) as artemisinins have been found to be the most potent antimalarial drugs and they have an excellent safety profile (Federal Ministry of Health, 2004).

However, the problem of availability and affordability still existed. Partners were therefore encouraged to prepackage ACTs which should be added to the market if found effective, approved and duly registered by the National Agency for Food and Drug Administration and Control (NAFDAC). One such combination drug is Artequin®, a combination of artesunate and mefloquine, manufactured by MEPHA Ltd (Aesch-Basel, Switzerland).

The rationale of adding mefloquine to artesunate is that due to the short half life of artesunate, a certain fraction of parasite may survive which is then exposed to long-term therapeutic concentration of mefloquine until complete extinction.

Mefloquine has been reported to consistently show high treatment efficacy in African Children (Sowunmi and Oduola, 1997; Steketee *et al*., 1996) and in pregnant women (Sowunmi *et al*., 1996).

Mefloquine, a 4-quinoline carbinol was reported to be one of the most effective drugs in the treatment of malaria in Nigeria (Schwatt, 1986). It was also found to be an outstanding suppressive prophylactic drug when administered weekly or fortnightly against drug-resistant *P. falciparum* (Karbwang and White, 1990). The successful treatment of falciparum malaria with regimens of artemisinin derivatives plus mefloquine has been reported in other countries (Looaresuwan *et al*., 1994; Price *et al*., 1997; Massousgbodji *et al*., 2002). The pharmacokinetics of mefloquine combined with artesunate in children with acute falciparum malaria in Thailand has also been studied (Nosten *et al*., 2000).

Li *et al*. (1994) showed that artesunate has a broader stage-specificity of action than other antimalarial drugs. After oral artesunate, relative bioavailability of the drug was 82%. The Parasite Clearance Time (PCT) and Fever Clearance Time (FCT) were 6.5 and 24 h, respectively (WHO, 2003) and parasitaemia was reduced by 90% within 24 h after starting treatment.

Having reviewed the study done by researchers in other countries and knowing that results of therapeutic efficacy tests (DTET) could depend on various parameters in any particular country and/or geographical zone of one country, we deemed it pertinent to undertake the clinical trial in a rural, high transmission area, Ijede community in Ikorodu Local Government Area of Lagos State.

- To evaluate therapeutic efficacy of a combination of Artesunate + mefloquine (Artequin®) in adults and children using the modified WHO 7 day *in vivo* test extended to 14 and 28 day-follow-up period.
- To determine the safety and tolerability of Artequin® (Artesunate + Mefloquine) in the treatment of acute uncomplicated malaria.
- To estimate gametocyte carriage and its reduction during treatment.

There is convincing evidence that a combination of two or more schizonticidal drugs will not only improve cure rate but could help reduce the rate of development of parasite resistance to either of the drugs in the combination. Furthermore, a combination of short-acting artemisinin derivative (artesunate) and long acting mefloquine are said to present a good ACT combination. Since no two populations are exactly the same, it is important to determine the safety, tolerability and efficacy of this ACT among Nigerian population. There is also the need to provide more ACTs as armamentarium for malaria control in Nigeria.

MATERIALS AND METHODS

Study site

Ijede: Ijede is a rural community in Ikorodu LGA which is about 10 km north of Ikorodu town and 30 km from Lagos State, Nigeria. Ijede has a population of about 14,000. The population is rather homogenous consisting primarily of peasant farmers and a few fishermen. It has 4 primary and two secondary schools. The community is fed by a good access road, good pipe-borne water and electricity supply. Apart from the Primary Health Centre, there is also a Private Clinic and a staff clinic at Egbin Power Station. The population of Ijede is well motivated for clinical trials, having been exposed to similar trials in the past. Ijede is considered to be a high malaria transmission area, hence its suitability for trials of this nature.

Entry criteria

Inclusion: Age stratified into 6 months-15 years (15-30 kg) and over 15 years (>30 kg), absence of severe malnutrition by clinical examination and weight for height measurement, mono-infection with *P. falciparum* parasitaemia with a parasitaemia in the range of 1000 to 250,000 asexual parasites per μL of blood, presence of axillary temperature ≥37.5°C and/or history of fever in the preceding 24 h, informed consent by parent/guardian (in the case of children), ability to come for the stipulated follow-up visits and, easy access to the health facility.

Exclusion: Presence of general danger signs such as: Not able to drink or breastfeed, vomiting everything, recent history of convulsion, lethargic or unconscious state, unable to sit or stand up and use of any drug known to influence cardiac function (e.g., Halofantrine) within 4 weeks before screening. Also excluded were those showing signs of severe and complicated falciparum malaria, namely, cerebral malaria (unarousable coma), severe anaemia (PCV <15% at day 0), renal failure (serum creatinine >3 mg dL^{-1}), pulmonary oedema, hypoglycaemia (<40 mg dL^{-1}), shock (systolic BP<70 in adults, 50 in Children), spontaneous bleeding, macroscopic haemoglobinuria, jaundice (serum bilirubin >3 mg dL^{-1}), febrile conditions caused by diseases other than malaria and History of allergy to study drugs.

Study design: No existing medication was approved for a direct comparison, so, a cross-sectional open label, non-comparative trial of three-day regimen of a combination of Artequin® (artesunate + mefloquine) for efficacy, safety and tolerability was carried out in Lagos State, Nigeria. Patients who met the criteria as earlier stated were asked to freely volunteer for the study. They or their guardians also gave written consent after explanatory notes. Day 0 was the day of screening, clinical assessment, initial malaria smears and taking of blood for Packed Cell Volume (PCV). The participants in each arm (adults and children) also had their blood taken for studies on the laboratory indices of safety, namely, routine biochemistry (Liver Function Tests such as aspartate amino-transferase (AST), alaninie amino-transferase (ALT), total and conj. bilirubin and urea) and Full Blood Counts (FBC), namely WBC, Platelets, ESR, PCV and reticulocytes. They were allocated to one or two bodyweight groups (15 to <30 and >30 kg) and given the first dose of artequin® (300/375 or 600/750 Lactab, respectively) on day 0.

The drugs were administered under medical supervision and treated patients were observed for 60 min. If vomiting occurred within 30 min of administration of the drug, the same dose was repeated. However, if it occurred 30-60 min, half the dosage was given again. Further vomiting entailed protocol violation. The patient was excluded and rescue treatment (with a locally effective antimalarial drug) was used. Any use of concomitant medications (including acetaminophen i.e., paracetamol) were documented in the Case Report Form (CRF).

After drug administration on day 0, the patients were asked to return on days 1 and 2 to complete the drug regimen and for clinical assessment. They were also given appointment papers for days 3, 7, 14 and 28 for clinical examination and blood smears. Blood was taken for PCV, LFT and FBC on each of these visits. They were also asked to return to the clinic on days other than these if they developed any additional complaints, or any change

in their condition compared to pre-administration of the drug. If a patient did not report at the Health Centre for the scheduled visit, every effort was made by the field workers to locate his/her home address.

Discontinuation of treatment: Adverse events, unsatisfactory therapeutic effects, loss of patient to follow-up, patient non compliance or consent withdrawal or withdrawal as a result of treatment failure, were criteria for discontinuation. All discontinued patients were followed-up for 28 days for safety assessments, where possible.

Efficacy assessments: Treatment efficacy was determined based on parasitological cure rates on days 3, 7, 14 and 28, by the times to parasite and fever clearance; and from the proportion of patients without gametocyte. Recrudescence denoted clinical recurrence of malaria after the initial clearance of parasite from the circulation. Parasite reappearance was interpreted as either true recrudescence or a new infection. Thus, treatment efficacy for cure rates in our context were described as uncorrected since no DNA Polymerase Chain Reaction (PCR) analysis was performed.

Safety assessments: All adverse events were monitored and recorded on the CRFs. Treatment-emergent symptoms of malaria were defined as adverse events occurring anew or worsening from baseline, but occurring before possible recurrence of parasitaemia.

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 follow-up visits.

Samples size calculation: The sample size of patients being used for this drug was calculated from the table of anticipated proportion (WHO/HTM/RBM/2003) at 95% confidence level and 10% precision. Calculation was based on estimated cure rate for current artemisinin-based antimalarial drug treatment (FMOH, 2004). With this combination drug having anticipated proportion of treatment failure of less than 5%, the sample size for the trial drug should be 18 (EPI-INFO version 6.04). However, since a minimum sample size of 50 is recommended by the World Health Organization (WHO), we decided to enroll about 60 patients on each arm (children and adults) making a total of 120 patients for the drug therapeutic efficacy test as we had to adjust for losses and withdrawals.

Parasite counts: At screening prior to enrolment, thick and thin blood films were examined. A second, Giemsa stained thick film was examined with a binocular microscope with an oil immersion objective lens to quantify the parasitaemia. Parasitaemia was measured counting the number of asexual parasites against a number of leukocytes in the thick blood film, based on a putative count of 8000 leukocytes per microlitre of blood or an adequate mean WBC in the population under investigation. The number of asexual parasites was counted against 200 leukocytes using a hand tally counter. The parasite per microlitre of blood was calculated by using the formula:

$$\text{Parasite Density (parasites } \mu L^{-1}) = \frac{\text{No. of parasites} \times \text{WBC count (8000)}^*}{\text{No. of leukocytes counted (200)}}$$

If *P. falciparum* gametocytes were seen, a gametocyte count was performed against 1000 leukocytes (WHO/MAL/82.988).

Temperature: Axillary temperature was recorded using a digital electronic thermometer.

Ethical Issues: This study was approved by the Ethics Review Board (IRB) of the Nigerian Institute of Medical Research (NIMR) who gave written permission to carry out the study. The Community Head and authorities of Ijede Health Centre also consented to the conduct of the study. The study was carried out in accordance with the principles laid down by the World Health Assembly of 1975 on Ethics in Human experimentation and the Helsinki Declaration. The study adhered to Good Clinical Practices (GCP) and conformed to the TDR Standard Operating Procedures (SOP).

Each, participant was informed of the aims, methods, anticipated benefits and potential hazards of the study. Then, informed, written consent was obtained by the investigator from every participant or parent/guardian of patients participating in the study. Verbal consent was acceptable but this was documented. The subject was informed that he/she was at liberty to abstain from participation in the study and that he/she was free to withdraw the consent of participation at anytime. This was written in English and Yoruba (the local language).

RESULTS

General: A total of 1453 patients were screened because they complained of symptoms suggestive of malaria and had not taken any antimalarial medication within the previous seven days. Overall, 120 patients fulfilled the criteria for enrolment but a total of 115 patients completed the study.

The, demographic and clinical characteristics of the patients are shown in Table 1.

Defaulters: A total of 115 enrolled patients consisting of 58 adults weighing 30 kg and above and 57 children weighing 15 to <30 kg completed the study.

However, 5 patients defaulted as a result of withdrawal/loss to follow-up and/or protocol violation. The study protocol is shown in Fig. 1.

Efficacy of artequin ®

Parasite clearance rate, profile and time: Results showed that on D I, 38 of the 58 enrolled adults and 13 of the 57 enrolled children no longer had any malaria parasites in their blood. The mean parasite densities in the remaining 27 adults and 44 children were drastically reduced. The clearance rate dramatically increased to 94.8 and 98.2% in adults and in children, respectively on D 2 until total clearance was achieved in the remaining 4 patients on D 3.

Table 1: Demographic and Clinical characteristics of Patients at enrolments (Day 0)

Characteristics		Group 1 Adults ≥30 kg	Group 2 child 15-29 kg
Sex ratio	Male	11 (19.0%)	36 (63.2%)
	Female	47 (81.0%)	21 (36.8%)
Mean age (Years) SD, (ranges)		23.40±11.96 (11-65)	6.83±2.47 (3-11)
Mean weight (kg) SD, (ranges)		51.93±13.24 (31-94)	19.84±4.42 (13-24)
Mean Height (cm) SD, (ranges)		158.64±8.05 (140-177)	116.14±16.81 (39-147)
Mean Parasite Density (μL^{-1})		22,541.91±42090.1 range (1028-220,000)	35,472.9±39,628.3 (1834-214316)
Mean axillary temperature	(°C)		
(n = 32)	<37.5°C n = 40	36.28±0.57	36.59±0.37
(n = 25)	≥37.5°C n = 18	38.54±0.62	38.82±0.77

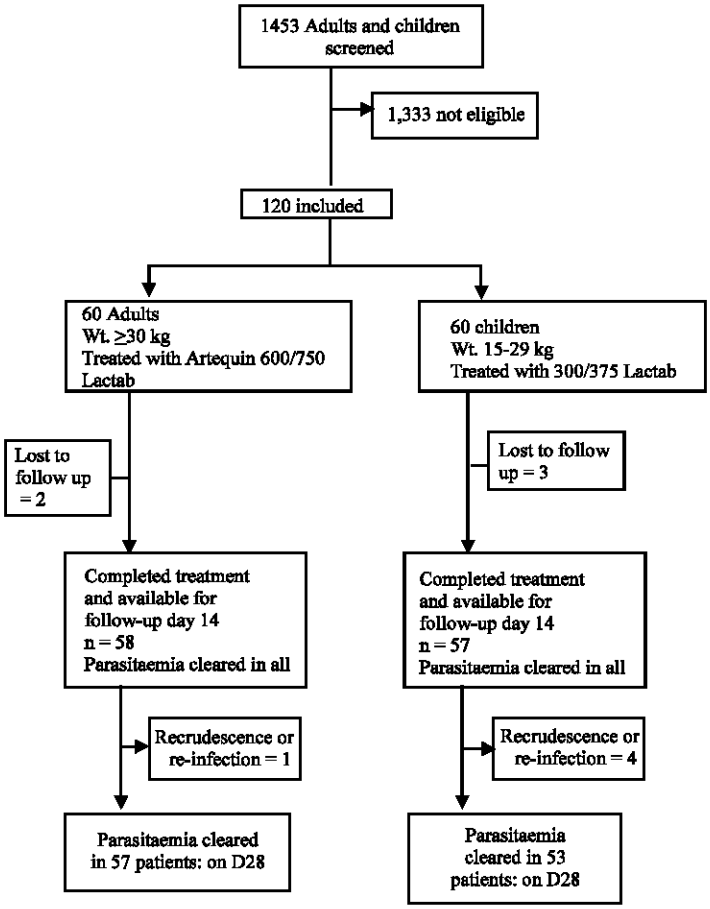

Fig. 1: Artequine® trial profile

In adults, the geometric mean parasite density of the 58 enrolled patients on day 0 was 7,377.19 which decreased to 19.39 on D1, therefore giving a percentage success rate of 99.7% (Fig. 2). The success rates on other days (i.e., using the geometric mean parasite densities) were as follows: D2 (94.8%), D3 (100%), D7 (100%) and D14 (100%). However, on day 28, one of the adults manifested low-grade parasite density of 360 parasite μL^{-1} blood. We were unable to infer whether it was as a result of recrudescence or of new infection since no Polymerase Chain Reaction (PCR) technique was used.

Time to Parasite Clearance (PCT) in 58 adults was determined from the spread sheet data (WHO/MAL/82.988). Parasitaemia completely cleared in 31 patients within 24 h, 24 cleared in 48 h while 3 patients were cleared in 72 h. Time to parasite clearance was therefore calculated as follows:

$$\frac{(31\times 24)+(24\times 48)+(3\times 72)}{58}=\frac{2112}{58}=36.4\text{ h}$$

In children, the geometric mean parasite density of the 57 enrolled patients on day 0 was 19,137.68 which reduced to 127.91 on D2 therefore giving a percentage success rate of 99.33% on D1 (Fig. 1)

The success rate on other days, using the geometric mean parasite density, were as follows: D2 (98.2%), D3 (100%), D7 (100%) and D14 (100%). As in adults, 4 of the children manifested low-grade parasitaemia on day 28 and had to be referred. Time to Parasite Clearance (PCT) in 57 children was also determined from the spread sheet. Here, parasitaemia had cleared in 13 children within 24 h (D1), 43 children within 48 h (D2) and in the remaining child within 72 h (D3).

Time to parasite clearance was therefore calculated as follows:

$$\frac{(13\times 24)+(43\times 48)+(1\times 72)}{57}=\frac{2448\text{ h}}{57}=42.9\text{ h}$$

Temperature clearance profile: Result showed that 40 of the 58 enrolled adult patients had temperatures below 37.5°C reflecting a possible self-medication with analgesics before coming to the health centre with high parasitaemia. The mean temperature of the 18 adult patients with temperatures ≥37.5°C was 38.54±0.58. The temperature dropped to a mean value of 36.41±0.74°C in 24 h. Therefore, the time to fever clearance (FCT = time from the first dose for the temperature to fall below 37.5°C and remain so for 3 consecutive days) was calculated to be 11.75 h (Fig. 3).

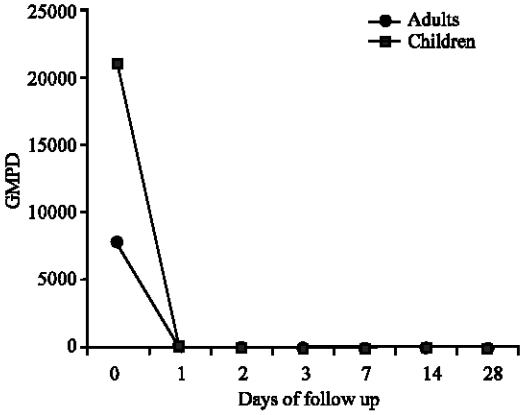

Fig. 2: Geometric Mean Parasite Density (GMPD) relative to days of follow up

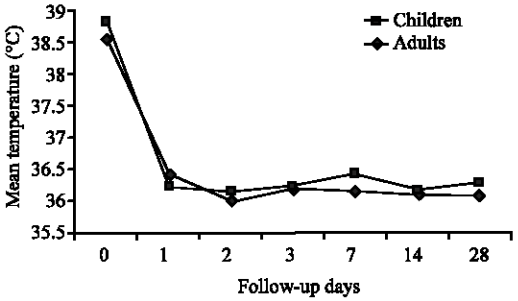

Fig. 3: Temperature clearance profile

The mean temperature of 25 children who were febrile (T≥37.5°C) was 38.82±0.77°C. The temperature of these patients dropped to 36.22±0.34°C by D1 (24 h). The time to fever clearance was calculated to be 12.25 h.

Anti-gametocyte activity: The mean gametocyte count dropped from pre-treatment values on day 1. However, more patients had gametocytes on D 2 although the overall mean value was lower.

The gametocytes were ultimately cleared by the second or third day of detection in the blood film. The gametocytes cleared in 3 patients in 24 h, one cleared in 48 h and 4 cleared in 72 h. Time to gametocyte clearance was calculated (as in parasite clearance time) to be 51 h.

Safety and tolerance: Artequin® was well tolerated. Adverse effects were carefully investigated according to the protocol. No Severe Adverse Effect (SAE) was reported during the study. Many AEs of the antimalarial drugs were most likely related to the underlying malaria disease. Two patients reported vomiting within 60 min of drug intake. A second set of drugs was administered and the patients were able to complete the trial. Three patients

Table 2: Laboratory characteristics of patients at enrolment (day 0)

(Children) body wt.	Group 1 (Adults) ≥30 kg	Group 2 15- 30 kg
Packed Cell volume (PCV%) (n = 46)		
Male	33.61±4.80	31.95±5.50
Female	38.82±4.96	31.56±3.95
Erythrocyte Sedimentation Rate (ESR) (n = 24)	41.86±29.6	51.29±32.26
Haemoglobin mg/L (n = 24)	11.39±1.87	10.63±1.78
Total White Blood Cells (WBC) (n = 24)	983.33±2160.05	8444.64±3043.67
WBC Differential (%) n = 24		
Lymphocytes	43.00±15.86	41.36±16.28
Neutrophils	58.29±13.73	58.25±16.37
Monocytes	2.33±2.20	1.50±1.37
Eosinophils	1.38±1.88	0.75±0.84
Alkaline phosphatase	183.67±83.08	200.84±55.9
Aspartate amino-transferase	4.05±3.17	5.70±3.47
Alanine aminotransferase	3.51±2.69	3.33±2.40
Total bilirubin	1.18±0.52	1.14±0.50
Conjugated bilirubin	0.39±0.26	0.40±0.32
Urea	17.98±6.31	15.58±6.30
Creatinine	0.94±0.31	0.80±0.36
Glucose	98.36±19.48	93.92±22.29

Table 3: Characteristics and study outcome of trial participants

Characteristics/Outcome	Artequin® (600/750) for adults >30 kg	Artequin® 300/375 for children 15-30 kg
Number enrolled	60	60
Number completed	58	57
Withdrawal/loss to follow up	2	3
Early Treatment Failure (ETF)	0	0
Late Clinical Failure (LCF)	0	0
Late Parasitological Failure ((LPF)	0	0
Adequate Clinical and Parasitological response (ACPR) Day 14	58 (100%)	57 (100%)
Adequate Clinical and Parasitological response (ACPR)* Day 28	57 (98.3%)	53 (93.0%)
Fever clearance time	11.75	12.25
Parasite clearance time	36.4 h	42.9 h

Polymerase Chain Reaction (PCR) uncorrected

experienced mild gastro-intestinal tract AE which occurred from D1 to D3. Two patients also reported that they experienced dizziness. All other AEs showed no relevant treatment groups. There were blisters in the mouth and a case of measles in a child by day 28 although this was not thought to be caused by the drug intake.

Laboratory indices of safety: The result of laboratory characteristics of patients at enrolment is shown in Table 2. The values in individual patients varied in accordance with the seriousness of the infection. However, the mean values of all parameters were within normal limits on D0. The WBC count showed slight increase in both infected adults and children. However, the increase was more prominent in the lymphocyte count with corresponding decrease in neutrophils as treatment progressed.

The increase in lymphocyte count from 37.92±16.25% on D0 to 61.65±11.45% on day 28 is consistent with manifestations of recovery in malaria infection. Here, immune mechanisms seemed to elicit cellular responses which rose against further infection.

The percentage reticulocyte count remained within normal limit for inhabitants of that area although normal values in some countries could be 0.2-2.0%. There was a slight decrease in mean haemoglobin value on days 7 and 14 before returning to normal on day 28. All these changes were not statistically significant ($p>0.05$). Only a few patients had PCV of over 40.0% at Ijede on D0. The mean value was 31.56±3.95 for men and 31.95±5.50 for women. However, there were decreases in the mean values on D7 and D14 before rising to the normal mean values for that period of investigation. Other haematological parameters, viz platelets, eosinophils and monocytes had varying values which were not statistically different ($p = 0.05$) from the D0 values.

The clinical chemistry values on D0 are also shown in Table 3. The mean starting values for total bilirubin was 1.12±0.62 μmol^{-1}. The level remained within this value from D0 to D28. There were also no significant decreases or increases ($p>0.05$) in the values of serum alanine aminotransferase (ALT, GOT), serum aspartate aminotransferase (AST, GPT) and alkaline phosphotase (ALK).

DISCUSSION

We have carried out the Therapeutic Efficacy Test on Artequin® at Ijede Community, Ikorodu LGA of Lagos State, Nigeria. The main outcome of our study was that a 3-d course with this artesunate-mefloquine blister pack is both highly effective and well tolerated in the treatment of acute uncomplicated *P. falciparum* malaria in Lagos State.

The geometric mean parasite density was reduced by 99.7% in adults and 99.33% in children within 24 h after treatment and completely cleared by day 3 in the 115 patients who completed the study. The adequate clinical and parasitological response in both adults and children were 100% in D3, D7 and D14.

The rapid clinical response was shown by a drop in temperature to normal values (viz., below 37.5°C) on the 2nd day. This rapid clinical and parasitological response confirmed the previous findings of others (Nosten *et al*., 2000; Li *et al*., 1994; Von Seidlein *et al*., 1997) who have, for many years worked in countries where, as in Nigeria, multidrug-resistant strains predominate.

Apart from the rapid clearance of asexual forms of *P. falciparum*, two observations added to the benefits of Artequin® therapy. First there was a significant reduction

in gametocyte count. The data suggest that artequin® ultimately cleared gametocyte from peripheral blood. This shows that artequin® exhibits considerable gametocidal effect. The second observation was that patients with mixed infections of *P. falciparum* and *P. malariae* were cured parasitologically and clinically.

It was observed in the course of this trial, that parasitaemia consisting of young trophozoites appeared on day 28 in one of the 58 adults and four of the 57 children. Parasitaemia was not associated with significant increase in body temperature. It was suspected that these could be new infections which are not unlikely in an area of intense transmission where a 28 day follow-up is being undertaken (Von Seidlein *et al*., 1997). Falade *et al*. (2005), by genotyping new infections seen between 2nd and 4th week post-therapy, attributed this phenomenon to new infections. There is therefore the urgent need to carry out more molecular genotyping of the parasite strains seen locally in Nigeria. This should indicate whether one is dealing with new infections or recrudescence.

It was also noted in the course of this study, that consenting to the taking of venous blood from patients for laboratory analysis was very difficult. Inhabitants did not like this aspect of the study at all. It was worse with adults. Coaxing and cajolery were tried but with caution so as not to go against ethical considerations. Nevertheless, we were able to complete the work amicably with the patients.

Artequin® from the experience of this study is safe and well tolerated. The laboratory values were not significantly different pre-and post-treatment. The marginal variations in liver function test results may be related to stabilization of the liver following successful treatment. The same result was observed with mean PCV values which returned to normal after recovery. The slight elevation in mean platelet count was consistent with the reported findings of relative thrombocytopenia in 50 to 75% of patients with acute malaria (Lee *et al*., 1997).

We conclude from this study that our results have confirmed the efficacy of artequin® in the treatment of *Plasmodium falciparum* malaria in Ijede, Ikorodu LGA, Lagos State which is in the South West Zone of Nigeria. It is also effective on mixed infections and exhibits significant gametocidal activity. As observed by other workers, the rapid parasitological response corresponded to the fast clinical response. Artequin® is well tolerated and safe. One of the advantages of this combination drug is the user-friendly, simple dosage regimen for adults and children and the acceptable taste which should improve compliance.

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