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Original Paper

Treatment of Uncomplicated Falciparum Malaria with Artesunate-Amodiaquine Combination Therapy (ACT) in a Rural Fishing Community in Sierra Leone

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ABSTRACT

Until recently, Chloroquine was the mainstay for malaria chemotherapy in Africa because it is cheap, safe and practicable for out-patient use. Resistance to this drug has however over the past decade, presented a major public health problem with therapeutic and prophylactic implications. As a response to the emergence of resistance to the commonly used antimalarial drugs, the World Health Organisation (WHO) now recommends the use of artemisinin-based combination therapies (ACTs). We assessed the therapeutic efficacy of oral Artesunate-Amodiaquine hydrochloride combination therapy in the treatment of uncomplicated falciparum malaria in a rural fishing community in Sierra Leone. One hundred and fourteen (114) participants aged 0 – 5 years attending the Outpatient Department of Gbondapi Health Centre were screened for recruitment into the study of which 70 fulfilled the inclusion criteria. Artesunate-Amodiaquine hydrochloride combined drug which passed the general counterfeit test of the Ministry of Health and Sanitation was used in the study. Adequate Clinical and parasitological Response (ACPR) was observed in 97% of the study population. Mean parasite clearance time in the participants with ACPR was found to be 24 hours (range 24 –72 hours). All 3% of the treatment failures were observed to be Early Treatment Failures (ETF). Results from the study indicate that Artesunate-Amodiaquine hydrochloride combination therapy is an effective antimalarial drug in a high transmission zone like Sierra Leone, and in the event that the drug is not effective, the results will be evident within one day of commencement of treatment.

Keywords: Artesunate-Amodiaquine, Falciparum, Therapy

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INTRODUCTION

Malaria has been reported as the leading cause of death in most countries in sub-saharan Africa with children below five years bearing the most morbidity and mortality (Taylor et al., 1993). Until recently, chloroquine was the mainstay for malaria chemotherapy in Africa because it is cheap, safe and practicable for outpatient use (Sahr *et al*., 2004). Resistance to this drug and other antimalarial drugs has however over the past decade, presented a major Public Health problem with therapeutic and prophylactic implications (Sahr et al., 2001). There is accumulating evidence that diminished sensitivity of the Plasmodium parasites to these commonly used antimalarial drugs is spreading (Simon *et al*., 1988; Oduola *et al*., 1989; Brasseur *et al*., 1992; Sowunmi and Oduola, 1997), and hence, strategies to prevent further spread and the availability of treatment options are urgently required. One such drug introduced for the treatment of multidrug-resistant falciparum malaria is artemisinin.

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The susceptibility of *Plasmodium falciparum* to artemisinin has been well established (Elhassan *et al*., 1993; Von Seidlein *et al*., 2000), and its effectiveness in the treatment of falciparum malaria in Africa has also been well documented (White *et al*., 1992; Elhassan *et al*., 1993; Taylor *et al*., 1993; Sowunmi and Oduola 1998).

Recent reports suggest an emergence of decreased sensitivity of the malaria parasite to artemisinin when used as monotherapy (Gay *et al*., 1994; Sahr *et al*., 2001). As a response to the emergence of such resistance, the World Health Organisation (WHO) now recommends the use of artemisinin-based combination therapies (ACTs) (WHO, 2006). Three such combinations commonly use in Sierra Leone are artesunate-amodiaquine, artesunate-lumefantrine and artesunate-sulfadoxime-pyrimethamine combinations. There is no available data on the efficacy of these combination drugs in Sierra Leone, but limited data collected by the Ministry of Health and Sanitation suggests that failed treatment to these newly introduced artemesinin-combinations is very rare (unpublished data). The objective of the present study is therefore to assess the therapeutic efficacy of oral Artesunate-Amodiaquine Hydrohloride combination therapy in the treatment of uncomplicated falciparum malaria in a rural farming and fishing community in Sierra Leone.

PARTICIPANTS AND METHODS

Study Site and Population

The study was conducted in Gbondapi village which is an established fishing settlement located in the Mao Sakrim Chiefdom, Pujehun District in the Southern Province of Sierra Leone. The village is divided into 3 communities – Gbondapi, Mani and Sumbuya and is bordered on the east by the Yakemo Kpukumu Krim and Kpaka Chiefdoms, on the South by the Atlantic Ocean, northwest by Kwamebai Chiefdom and on the North by Panga Krim Chiefdom. Because of the very close proximity between Mani and Sumbuya, and the relatively few participants registered from Sumbuya, all the participants from this community were registered under Mani. Majority of the 5,000 residents speak mende, creole and a few speak English. There is a government assisted health centre in the village that is supervised by a Community Health Officer, with referrals often made to the district Hospital in Pujehun town that is 80 kilometers away. Malaria transmission in this area is high and peaks during the rainy season. The village depends on a few hand-pump wells and unprotected streams for domestic water use, and poorly built pit-latrines for adults while children defecate indiscriminately between houses.

Sample Collection and Examination

Data was collected from the Primary Health Centre. The Health Centre serves all age groups in the three communities and subjects enrolled for the study were children below 5 years attending the Gbondapi Health Centre. The WHO Protocol (WHO 2003) for the recruitment of participants in therapeutic efficacy trials in high transmission zones was applied. The inclusion criteria were: Children below 5 years, temperature ≥ 37.5^{o}C, mono-infection with *Plasmodium falciparum*, parasitemia ≥ 1000 parasites/µl of blood and Informed consent from accompanying parents. Participants with severe or complicated malaria according to the WHO classification (WHO 1996) were excluded from the study and treated with parenteral quinine dihydrochloride. Arteunate-Amodiaquine hydrochloride combined drug which passed the general counterfeit test of the Ministry of Health and Sanitation was used in the study. Each tablet of Artesunate contained 50mg Artesunate and each tablet of Amodiaquine hydrochloride contained 150mg Amodiaquine. The test drug was administered orally over a three day period under the direct supervision of Community Health Officer (CHO) in the following dosages as directed by the manufacturers (Guilin Pharmaceutical Co. Ltd. China):

Adults:	2 tablets of Artesunate with 2 tablets Amodiaquine hydrochloride 12 hourly for three days
7 – 13 years:	1 tablet Artesunate with 1 tablet Amodiaquine hydrochloride 12 hourly for three days.
1 – 6 years:	Half tablet Artesunate with half tablet Amodiaquine hydrochloride tablet 12 hourly for three days.

All participants were followed-up on days 1, 2,3,7,14,21 and 28 during which the child's general condition was assessed and blood smear prepared for the assessment and demonstration of malaria parasites.

Axillary temperature of all each participant was also recorded on each of the follow-up days. The response to the test drug was recorded according to the recommendation of the WHO (WHO 1996): Adequate clinical and parasitological response (ACPR), Early Treatment Failure (ETF) and Late Treatment Failure (LTF). Briefly, ACPR was defined as the absence of parasitemia on day 14 irrespective of axillary temperature or axillary temperature less than 37.5^{o}C irrespective of parasitemia, without previously meeting any of the criteria of ETF. Therapeutic response was classified as ETF if the subject developed one of the following conditions during the first three days of follow-up.

a) Axillary temperature ≥ 37.5^{O}C on day 2 with parasitemia greater than that on day 0 or
b) Axillary temperature ≥ 37.5^{O}C on day 3 in the presence of parasitemia
or
c) Parasitemia on day 3 ≥ 25% of count on day 0.

Therapeutic response was classified as LTF if a subject had axillary temperature ≥ 37.5^{O}C in the presence of parasitemia on any day from day 4 to day 14 without previously meeting any of the criteria of ETF. All subjects with ETF and LTF were put on quinine sulphate 10mg/kg 8 hourly for at least five days.

Ethical Clearance

Ethical clearance for the study was obtained from the Research and Ethics Committee of the Ministry of Health and Sanitation.

RESULTS

A total of 114 participants were screened for enrollment into the study, of which 70 fulfilled the enrolment criteria. Laboratory data of the participants enrolled into the study is summarized in Table I. The mean age of the participants was 17.2 months and the mean parasite count on the day of enrolment (day 0) was 1264 parasites/µl of blood. The temperature of the participants on the day of enrolment ranged from 37.8-39.2ºC with a mean of 38.1ºC.

TABLE 1: Laboratory data of participants enrolled in Artesunate-Amodiaquine Hydrochloride Combined Therapy efficacy study in Gbondapi and Mani

	Variable
No of subjects screened	114
No of subjects recruited	70
Age of subjects (months)	
Mean	17.2
Range	5 -60
Temp on day 0 (^{O}C)	
Mean	38.1
Range	37.8 – 39.2
Parasitemia on day 0 (Parasites/µl of blood)	
Mean	1264
Range	1006 – 2430

The therapeutic responses of the 70 participants enrolled in the study are summarized in Table 2. All 70 participants completed the 28 day follow up. The mean fever clearance time with the test drug was one day (range 24-72 hours), and the mean parasite clearance time was also 24 hours (range 24-72hours).

Table 2: Summary of the Therapeutic Response of Participants enrolled in Artesunate-Amodiaquine hydrochloride Combined Therapy Study

	Variable
No enrolled in study	**70**
No completed in study	**70**
Fever clearance time (hours)	
Mean Range	**24** **24 – 72**
Parasite clearance time(hours) of children with adequate clinical response	
Mean Range	**24** **24 – 72**
No (%) of subjects with Adequate Clinical Response (ACPR)	**68 (97)**
No (%) of Subjects with Early Treatment Failure (ETF)	**2 (3)**

Adequate Clinical Response (ACPR) to the drug was observed in 97% of the participants with only 3% showing treatment failures. According to the WHO classification of treatment failures (WHO 2003), all 3% treatment failures were observed to be Early Treatment Failures (ETF).

DISCUSSION

Because resistance to the commonly used antimalarial drugs is a global problem, Artemisinin–based combination therapies (ACTS) are now the first-line therapies in most malaria-endemic countries. The commonly used artemesinin-based combination therapies in the treatment of uncomplicated falciparum malaria are Artemether-mefloquine and Artemether-lumefantrine (WHO, 2006). Another available Artemesinin combination is the Artesunate-Amodiaquine, which is recommended by the Ministry of Health and Sanitation of Sierra Leone as the first-line drug in the treatment of uncomplicated falciparum malaria.

The results of this study suggest that Artesunate-Amodiaquine combined therapy is highly efficacious in the treatment of falciparum malaria in Sierra Leone as evidenced by the 97% clinical response obtained. Recent clinical and molecular studies suggest the emergence of ACT-resistant *Plasmodium falciparum* infections in the Cambodia-Thailand border area, were the standard ACT is Artesunate-mefloquine combination (Wongsrichanalia *et al*., 2000). It was suggested that treatment failures observed in that study might be due to the high-level mefloquine resistance, as mefloquine was used as monotherapy in the treatment of falciparum malaria long before the introduction of ACT.

Sahr *et al*. (2001) have reported 4 cases of apparent drug failure in Sierra Leone with the use of Artesunate as monotherapy. The four cases described indicate that although Artesunate is a safe alternative drug to Chloroquine, resistance to it is slowly emerging on the African continent. Using the criteria of the World Health Organisation in the classification of treatment failures, no late treatment failures (LTF) were observed within our study population. This indicates that in the event that Artesunate-Amodiaquine combined therapy is not effective, the result will be known within a day of commencement of therapy. The Artemisinins are characterized by a rapid reduction of parasitemia which begins almost immediately on commencement of treatment with complete clearance usually occurring within 48 hours. Several reports suggest that radical cure can be achieved with the Artemisinins when they are combined with other antimalarial drugs (Looareesuwan *et al*., 1992; Nosten *et al*., 1994; Prince *et al*., 1995; Von Seidlein *et al*., 2000).

Results of a survey conducted in the capital Freetown among pharmacies on the sale of antimalarial drugs revealed that Artesunate ranks high in the list with most of the drug sold without prescriptions (Sahr *et al*., 1999).

It is thought that if the unregulated use of Artesunate or its combined antimalarial drugs continues, there is a high tendency of enhancing the development of resistance to the drug among the Sierra Leonean population. It is therefore recommended that measures are put in place by the Ministry of Health and Sanitation to restrict the distribution and sale of Artesunate-combination drugs so as to reduce the tendency of the development of resistance to the drug.

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