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Full Length Research Paper

Efficacy and safety of artemisinin – naphthoquine (ARCO®) in the treatment of uncomplicated *Plasmodium falciparum* among Sudanese adults

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Although artemisinin combined therapies (ACTs) offer great hope for Africa in controlling malaria, the ideal combination regimen remains uncertain. ARCO is a single dose treatment and proven to be efficacious, so this study aimed to assess the safety and efficacy of this new generation ACT in the treatment of uncomplicated *Plasmodium falciparum* among Sudanese adults. From November 2006 to March 2008, the efficacy and safety of Artemisinin + Naphthoquine (ARCO) in the treatment of uncomplicated *Plasmodium falciparum* was investigated in Eastern and Central of Sudan. 129 patients were enrolled in this study, and were treated with ARCO. All patients were followed up for 28 days according to the WHO-*in vivo* protocol-2003. The results obtained by ARCO study revealed that the fever clearance time (FCT) was (12.0 +/- 4.8 hours) and parasite clearance time (PCT) was (34.8+/-12.6 hours), Overall clinical and parasitological outcome showed that adequate clinical and parasitological response (ACPR) was 120/122 (98.4%), early treatment failure (ETF) was 0/122 (0%) and late clinical and parasitological failure (LCPF) was 2/122 (1.6) and no Gametogenesis was observed during the follow-up days. ARCO proved to be an effective ACT, was very safe and well tolerated, no adverse reaction detected -There was no new events and no adverse effects on bone marrow

Keywords: Sudan, malaria treatment, ACT, ARCO.

INTRODUCTION

Background

Due to the increase resistance of malaria parasites to the conventional antimalarial drugs including chloroquine, sulphadoxine/pyrimethamine and mefloquine, The World Health Organization has endorsed artemisinin-based combination therapy (ACT) as first-line treatment. ACTs produce a very rapid therapeutic response and are well tolerated by patients. And also have the potential to reduce transmission of malaria and the parasite is

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unlikely to become drug resistant. 56 endemic countries, 34 of them in Africa, have officially adopted ACTs as their first line of treatment since 2004 (WHO, 2006). The use of chloroquine and sulfadoxine-pyrimethamine as partners in ACT may only have value as a short-term measure in patients with a degree of immunity to malaria. The current available partners include mefloquine, lumefantrine and piperaquine. Artesunate-mefloquine is highly effective but is expensive and side effects can be problematic. Artemether-lumefantrine, is expensive and needs to be administered with food to ensure adequate bioavailability. Dihydroartemisinin-piperaquine is highly effective, well tolerated and relatively inexpensive (Davis et al., 2005). Although ACTs offer great hope for Africa, the ideal combination regimen remains uncertain and cost is a problem. To compare the efficacy of the different therapies, bigger and longer controlled trials are needed in the different transmission patterns (Paul, 2005). So, a novel drugs such as pyronaridine or naphthoquine are needed to be tested as a partner in ACT. The naphthoquine phosphate is an antimalarial known as tetra-aminoquinoline, has a slower onset of schizonticidal action and a longer half-life and in contrast artemisinine has a rapid onset of schizonticidal action and a short half-life. The naphthoquine and artemisinine combination developed in China, and called ARCO (Wang et al., 2004). These two components act synergistically in animal, and clinically provide more rapid relief of symptoms and a higher cure rate than either component alone. ARCO is a safe drug, tolerable, effective and affordable, with a short course of only one dose. The previous ARCO clinical trials in China showed 97% cure rate and clear 97.5% of malaria parasites within 24 hours (Wang et al., 2002; Wang et al., 2003), and 99% cure rate was reported from Thailand (Krudsood et al., 2003), Further ARCO clinical studies were conducted in malaria endemic countries, in Uganda showed high efficacy (Bukirwa et al., 2006), while 94%, 98.8% and 100% cure rates were reported from Papua New Guinea (Hombhanje et al., 2009), Benin (Kinde-Gazard et al., 2012) and cote d'Ivoire, (Toure et al., 2009) respectively. In Nigeria this new ACT when assigned to the dose of 700 mg 12-hourly doses showed 93.1% cure rate (Martin et al., 2012), In Sudan, malaria is endemic and it is a major health problem and the whole population are at varying degrees of risk. The most important change in malaria treatment policy is shifting from conventional antimalarial drugs to combination therapy using ACT as a first and second line treatment since 2004 (National Malaria Control Program (NMCP) 2004). The clinical trials conducted on these new recommended ACTs in the national drug policy, artesunate-sulfadoxine-pyrimethamine (AS/SP) (Sakina et al., 2005; Adam et al., 2006; Mukhtar et al., 2007; Mohamed et al., 2006), artemether-lumefantrine (AL) (Mohamed et al., 2006; Mukhtar et al., 2007), and other ACTs, artesunate-mefloquine (ASMQ) (Adam et al., 2005) and artesunate-amodiaquie (ASAQ) (Ibrahium et al., 2007) showed very encouraging cure rates ranging from 94.7% -100% in eastern and central Sudan. The aim of this study was to assess the efficacy, safety and tolerability of fixed dose combination of ARCO for the treatment of uncomplicated falciparum malaria among adolescents and adults in Sudan

MATERIALS AND METHODS

Study sites

This clinical trial was conducted in two regions of Sudan, In East Sudan*:* the study was carried out in New Halfa, Kassala State and Elgaria Ashara, Gedarif State. In Central Sudan*:* the study was carried out in Wad Medani, Gezira State. These study sites are located in irrigated agricultural schemes, where the transmission is high as identified by epidemiological strata of malaria in Sudan.

Patients and Treatment

Only adults infected with uncomplicated *P. falciparum* malaria, and meeting both the inclusion and exclusion criteria stated in the WHO *in vivo* protocol - 28 days follow-up-2003 (World Health Organization, 2003), were enrolled in this study.

Date of enrollment, the study site, patient serial number (SN), full name, sex (M/F), age (years), weight (kg), number of attacks of malaria and history of previous antimalarial therapy within the preceding 4 weeks, history of other medications, presenting complaints, guardian's name and contact address were written in special case records form.

In addition to the above information, on the initial day (D0), the followings were done for each patient enrolled: clinical assessment, including measuring the axillery temperature, thick and thin blood films were made in one slide and labeled with the SN, blood blotted filter paper were collected, T.W.B.Cs were determined, then the parasite count was made and recorded, the body weight was measured and recorded. Then all enrolled participants were treated with single dose of 8 ARCO tablets, receiving one dose of 400 mg of NQ and 1000 mg of ART (the drug used was manufactured by KUNMING PHARMACEUTICAL CORP. D.R. China – Batch No. 2005o637, Mfg Date 05/06/2005, Exp. Date 05/2008).

Then the patients were asked to report to the health centers for clinical and parasitological evaluation on the scheduled 28 follow-up days (i.e. on D1, 2, 3, 7, 14, 21 and 28).

Table 1. Baseline characteristics of the enrolled subjects infected with acute uncomplicated *Plasmodium falciparum* malaria and treated with ARCO® (n = 129)

Demographic characteristics	
Mean age (years)	36.27(20 – 60
Sex	90(M), 39 (F)
Clinical characteristics	
Mean Body weight (kg)	68.4 (42 – 95)
Mean Temperature on D0 (OC)	37.9(36.5 – 39.0)
Mean parasite count on D0 (/ µ of blood	5169(1200 – 14400)
Mean hemoglobin on D0 (g/dl)	11.9(10.7 – 13.3)

Samples collection

Samples were collected for all techniques mentioned below before treatment (D0) and post-treatment follow-up days.

For micrscopy, blood samples were collected from the participants and thick and thin blood smears were made on days 0, 2, 3, 7, 14, 21 and 28, and stained with 10% Geimsa stain for 30 minutes (World Health Organization, 1991). Microscopic examination were done by the investigators and rechecked by two independent malaria microscopists. All slides were coded and made available for quality control later.

Follow up and Assessment

According to the WHO *in vivo* protocol - 28 days follow-up 2003, the visits were scheduled on days 1, 2, 3, 7, 14, 21 and 28 for clinical and parasitological evaluation. The assessment outcomes were determined by the followings therapeutic efficacy:

Development of danger signs or severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitaemia classified as early treatment failure (ETF), the presence of parasitaemia and an axillary temperature > 37.0°C on any day between Day 4 to Day 28 classified as Late clinical and parasitological failure (LCPF) and classified as adequate clinical and parasitological response (ACPR) if the patient did not develop any of the criteria of ETF or LCPF.

During the follow up days, parasite clearance time (PCT), fever clearance time (FCT) were determined, the presence of gametocytes was checked in the blood films collected, hemoglobin level was estimated in D0 and D28. Tolerability was assessed by describing the new adverse events resulted from the tested drug (ARCO), liver enzymes and renal function were measured on D3.

Ethical approval

Ethical approval for this study was obtained from the ethical committee of the Blue Nile Research National Institute for Communicable Diseases - University of Gezir*a* and permission was obtained from the national malaria control program (NMCP) at the Federal Ministry of Health and the local health authorities in the states. The participants were only enrolled in the study after informed consent was obtained.

Sample size calculation

The sample size was determined based on the WHO standard protocol for non-comparative therapeutic efficacy studies (World Health Organization, 2003). For example, in the case of a test drug with an expected failure rate lower than 15%, a minimum of 50 patients should be included in order to be representative

Statistical analysis

Data generated were recorded in the case record forms, then entered and analyzed by statistical program SPSS for windows (version 11.0.1). The parasite clearance time (PCT) and fever clearance time (FCT) were determined by linear interpretation

RESULTS

From November 2006 to March 2008, in 3 study sites in eastern and central Sudan 129 patients infected with uncomplicated *P.falciparum* malaria were selected for this study. As indicated in table I, the enrolled cases were 90 males and 39 females aged between 20 – 60 years

Table 2. Clinical, Parasitological and laboratory outcomes following the treatment by ARCO® (n = 129)

Clinical characteristics		
Withdrawn	7/129(5.4%)	
Mean Temperature (OC) on:		
	D1	36.9
	D2	36.7
	D3	36.5
FCT (hours)	(12.0 +/- 4.8)	
Severe signs	0	
Serious adverse reaction requiring the trial withdrawal	0	
Parasitological characteristics		
Mean parasite count (/ µ of blood) on:		
	D 2	0
	D 3	0
	D 7	1.5
	D 14, 21 and 28	0
PCT (hours)	(34.8+/-12.6)	
Gametocytaemia during the follow-up days	0	
Biochemical and haematological characteristics		
Liver enzymes (on D3)		
Mean SGOT (U/L)	12.7(4 – 20)	
Mean SGPT (U/L)	10.5 (3 – 17)	
Mean creatinine level (mg/dl)	0.8 (0.6 – 1.2)	
Hemoglobin on D28 (g/dl)	12.4(11.1 – 13.6)	
Overall assessment outcome:		
ACPR	120/122(98.4%)	
ETF	0/122(0%)	
LCPF	2/122(1.6)	

with a mean of 35 .65 years, their body weight ranged between 42 -95 Kgs with a mean of 68.4 Kgs. On D0, the temperature measurement ranged between 36.5 – 39.0 ^{0}C with a mean of 37.9 ^{0}C, the parasites count determined ranged between 1200 – 14400 with a mean of 5169 parasites/ µ of blood and the Hemoglobin done ranged between 10.7 – 13.3 g/dl with a mean of 11.9 g/dl.

Following the treatment by ARCO, table 2 showed that 7/129(5.4%) were withdrawn from study and 122/129 (94.6%) reached the scheduled end point of 28 follow up day.

On D1, D2 and D3, the mean temperature decreased to 36.9, 36.7 and 36.5^{0}C respectively (figure I) and revealed that the FCT was (12.0 +/- 4.8 hours), and no severe signs or serious adverse event observed in all the enrolled subjects. The malaria parasite disappeared during the follow up days (D2, D3, D14, D21 and D28), and only 2/122 (1.6%) demonstrated malaria parasite on D7 with a mean count of 1.5 / µ of blood and revealed that the PCT was (34.8+/-12.6 hours) as indicated in table 2 and figure 2. And during the follow-up days no Gametocytaemia observed.

Biochemical and haematological findings on D3 showed that the liver enzymes: the mean SGOT was 12.7 (4 – 20 U/L), the mean SGPT was 10.5 (3 – 17 U/L), and the mean serum creatinine level was 0.8 (0.6 – 1.2 mg/dl), while the hemoglobin level on D28 ranged between 11.1 – 13.6 g/dl with a mean of 12.4 g/dl.

The overall assessment outcomes showed that the ACPR was 120/122 (98.4%), ETF was 0/122 (0%) and LCPF was 2/122 (1.6).

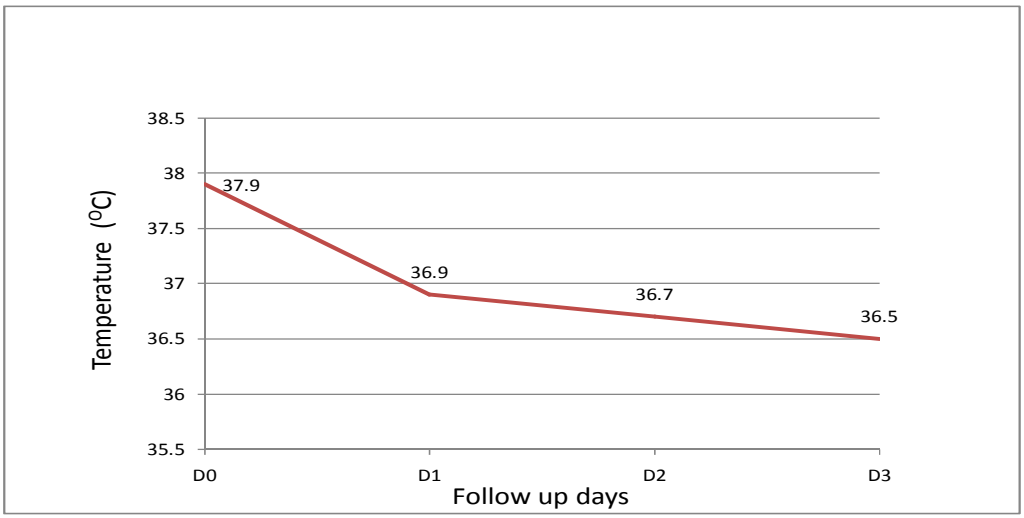

Figure 1. Fever clearance time (FCT)

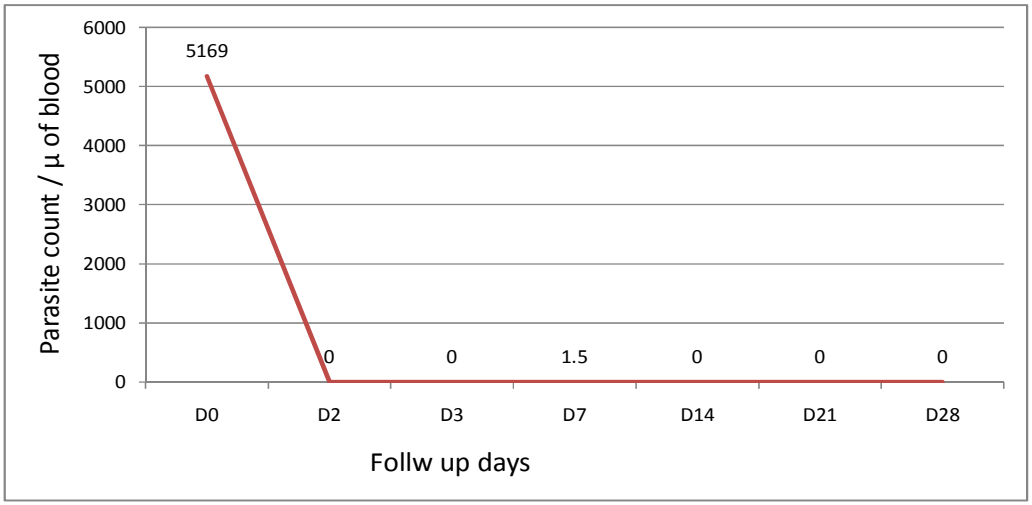

Figure 2. Parasite clearance time (PCT)

DISCUSSION

This is a first study of ARCO combination therapy in Sudan, it revealed 98.4% clinical and parasitological cure rate, This high cure rate when compared to that previously published research works of ACTs carried out in Sudan (table 3), it was less than reported on the first line treatment (AS/SP) in eastern Sudan by Sakina B. *et al*., 2005, Adam, IE. *et al*., 2006 and Mukhtar EA *et al*., 2007 in eastern Sudan, but it was similar to that reported in central Sudan by Mohamed AO *et al*., 2006. The cure rate found by this study when compared to that published before on the second line treatment (AL), it was less than reported by Mohamed AO *et al*., 2006 in central Sudan and more than reported by Mukhtar EA *et al*., 2007 in eastern Sudan. However, there is no a significant difference between the high cure rates (98.4 – 100%) found by this study and other previous studies conducted on the first and second line malaria treatment in Sudan. But when compared to that published on other ACTs, it was higher than reported in eastern Sudan by I Adam *et al*, 2005 and Ibrahium, A.M. *et al* , 2007 on AS/MQ and AS/AQ respectively.

In comparison with other studies conducted in the same ACT (table 4), the ARCO efficacy frequency revealed by this study, it was higher than reported in China by Wang SQ, *et al* 2002 and Wang JY, *et al* 2003 and slightly lower than reported in Thailand by Krudsoob S, *et al* 2003. This efficacy when compared with other findings in other malaria endemic countries, it was

Table 3. Previous Clinical Trials of ACTs in Sudan

ACTs tested	**Study site**	**Year**	**Clinical and parasitological cure rate**
AS/SP	Eastern Sudan	2005	99.3 %
	Eastern Sudan	2006	100%
	Eastern Sudan	2007	100%
	Central Sudan	2006	High efficacy
AL	Central Sudan	2006	100%
	Eastern Sudan	2007	Slightly high efficacy
ASMQ	Eastern Sudan	2005	94.7%
ASAQ	Eastern Sudan	2007	95.2%
ARCO (the current study)	Eastern and Central Sudan	2006 – 2008	98.4 %

Table 4. Previous Clinical Trials of ARCO (2002-2012)

Study site (Country)	**Year**	**Clinical and parasitological cure rate**
China	2002	97 %
	2003	97.5%
Thailand	2005	99%
Uganda	2006	High efficacy
cote d'Ivoire	2009	100%
Papua New Guinea	2009	94%
Benin	2012	98.8%
Nigeria	2012	93.1%
Sudan (the current study)	2006 -2008	98.4%

reported to be similar to that found in Uganda by Bukirwa H, *et al* 2006 and higher than attained in Papu New Guinea by Hambharje FW, *et al* 2009 and in Nigeria by Martin M Meremikwu, *et al* 2012. While it is lower than reported from cote d'Ivoire by Kinde-Gazaard D, *et al* 2009 and in Benin by Toure OA. *et al* 2006.

The ACPR (98.4%) and the ETF (0%) outcome achieved by this study and as reflected by the FCT and PCT determined was attributed to that the two components of ARCO, clinically provide more rapid relief of symptoms and a higher cure rate than either component alone and could combat the emergence of antimalarial drug resistance. In addition the short half-life of artemisinin achieves substantial and rapid parasite killing, while the long half-life of naphthoquine eliminates the remaining malaria parasites. The two cases that classified as LCPF (1.6%), showed parasitaemia in their blood films examined in D7 but when examined before in D2 and D3 there was no malaria parasites detected. The explanation of this difference was that the parasites densities are as low as the detection threshold (5 – 10 parasites/µl blood) which cannot be detected in the blood smears by microscope.

As in many clinical trials of ACTs, we observed that during the follow up days, no gametocytes were detected in the blood smears examined, so, the ARCO has the potential of reducing transmission.

In the current study, 7/129 (5.4%) were withdrawn, four decided to end their participation and three were lost to follow up, this low percentage of withdrawn (< 20%) does not affect the study validity.

In table 2, throughout the scheduled follow up days there were no severe signs or new events reported as well as there was no serious adverse reaction requiring the trial withdrawal. The renal and liver functions were within the normal values and not adversely affected. There was also no adverse effects on bone marrow and actually Hb% improved as an indication of that the ARCO was safe and well tolerated.

This new ACT has the advantage of being a fixed tablet foronsider mulation and easil Administered by the health providers and the patients themselves, it is superior to the first and second line treatment in Sudan and other existed ACTs by it is only one dose at once regime while the other ACTs are taken over 3 days regime.

In conclusion, ARCO proven to be effective ACT, safe and well tolerated and can play a role in overcoming drug resistance and reducing transmission, so, further studies to be conducted among children especially less than 5 years and in different malaria epidemiological strata are recommended.

Generally the outcomes of this study will encourage the stakeholders to consider ARCO as an option in any malaria treatment updating.

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