Therapeutic efficacy of sulfadoxine/pyrimethamine plus chloroquine and artesunate plus amodiaquine for the treatment of uncomplicated falciparum malaria.

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Abstract

Therapeutic efficacy and safety of sulfadoxine/pyrimethamine plus chloroquine as well as that of artesunate plus amodiaquine for the treatment of uncomplicated Plasmodium Falciparum malaria was conducted by the National Malaria Control Program with technical and financial support from the WHO. The study was conducted at 6 sentinel sites, each treatment combination used in 3 sentinel sites depending on the malaria disease burden.
The sulfadoxine/pyrimethamine plus chloroquine combination resulted in adequate clinical and parasitological response in 50.0% of cases with total treatment failure of 50.0% after the 28 day follow-up period which exceeded 10% the WHO recommended cut-off point at which countries are recommended to change antimalarial treatment policy.
The in-vivo therapeutic efficacy and safety baseline study on artesunate plus amodiaquine was conducted in the other 3 sites. After a follow up period of 28 days, adequate clinical and parasitological response was 96.6% whereas the total treatment failure was 3.4%, a failure rate acceptable for continuation of treatment option by the WHO. Thus, the results of the therapeutic efficacy study findings on chloroquine plus sulfadoxine/pyrimethamine for the treatment of uncomplicated falciparum malaria warrant an immediate change of the antimalarial treatment policy so that safe and the proven efficacious alternatives are incorporated into the treatment guidelines in Eritrea.

Introduction

Malaria is an endemic disease that is causing significant morbidity and mortality particularly in the Sub-Saharan African countries [1]. The African Heads of States pronounced the Abuja Declaration as a strategy to address the economic and morbidity effects of this disease [2].

One of the challenges facing the control of malaria has been the rapid development of drug resistance from the previously efficacious and cost effective chloroquine based drug treatments[3]. Indeed the WHO has provided technical guidelines to support member countries in identification of resistance and introduction of new drug formulations [4].

Although Eritrea has already achieved the Abuja targets for malaria control ahead of schedule, the challenge that is facing the country is the sustainability of these important gains[5]. Specifically the target of malaria elimination and the emergence of drug resistance are major constraints.

Eritrea has been conducting routine antimalarial treatment efficacy studies at specific sentinel sites since 1998. As a result of the operational research in these areas, it was possible to identify malaria resistance to chloroquine that prompted the change of first line treatment from chloroquine only to chloroquine plus sulfadoxine/pyrimethamine in 2002 [6].

Results from continuous monitoring of drug efficacy coupled with anecdotal reports of resistance from clinicians in the high malarious areas prompted the efficacy study on the existing drug treatment regimen. Other countries have recognized increasing resistance to the first line of treatment of chloroquine plus suladoxine/pyrimethamine and taken appropriate action based on the WHO recommendation[7]. One of the drawbacks for the introduction of the artesuante based combinations has been the high cost of the drug and short life.

The main objective of the study was therefore to systematically assess the therapeutic efficacy of sulfadoxine/pyrimethamine plus chloroquine; and artesunate plus amodiaquine for the treatment of uncomplicated falciparum malaria in Eritrea in order to guide policy.

Methodology and materials

With technical support from WHO Inter-Country Support Team for East and Southern Africa, the National Malaria Control Programme (NMCP) adapted the WHO "Assessment and Monitoring of Antimalarial Drug Efficacy for the Treatment of Uncomplicated Falciparum Malaria – 2003" and the "Practical Handbook for Antimalarial Drug Therapeutic Efficacy Testing for the Health Worker" in March 2006. WHO AFRO supported the training of health workers at the six sentinel sites in August 2006 utilizing these two documents.

Sulfadoxine/pyrimethamine plus chloroquine were studied in Sawa and Tesseney hospitals and Dubarwa health centre. Artesunate plus amodiaquine were studied in Engela, Goluj and Tokombia health centres (Figure 1).

Fig. 1: Map of sentinel sites for antimalarial drug efficacy studies in Eritrea

All members of the study throughout the regions were trained using the WHO 2003 guidelines and field guides prior to conduct of the study between September and December 2006.

Sulfadoxine/pyrimethamine plus chloroquine were administered at 3 sites while artesunate plus amodiaquine were used at the other 3 study sites. All the study drugs were provided by WHO HQ after quality control testing.

Patients aged more than 6 months with P. falciparum mono-infection and parasitaemia in the range of 1,000 - 100,000/µl on day zero, axillary temperature greater than or equal to 37.5°C or a history of fever during the last 24 hours, were able to come for the stipulated visits and consenting to the study were enrolled. Patients were excluded if they presented with general danger signs, severe malnutrition or presence of febrile conditions other than malaria, history of allergy or complaints to the drugs administered. Children under six months of age and pregnant women were not enrolled in the study.

The sample size (n) was determined using the formula n = (1 + 0.20) x 50 = 60 and adjusted for the follow up losses and withdrawals (expected to be 20% in studies with 28 days follow up). For each site an ideal sample of 60 was determined with a sample size of 50 still being acceptable.

All patients presenting with a history of fever and satisfying the inclusion criteria were enrolled after agreed consent and treated with sulfadoxine/ pyrimethamine plus chloroquine or artesunate plus amodiaquine according to body weight or age, under observation. They were followed up on Day 1, 2, 3, 7, 14, 21 and 28 or any unscheduled date for assessment. On each of these days, their clinical status and parasitaemia were assessed. Blood was collected on PCR stripes on Day 0 and any other day of parasitological failure after Day 7.

Data was entered by two independent persons into Epi Info to validate the results. The data in the first entry was validated. The second entry was the check for the first entry. The two entries were harmonized.

Results

A total of 203 patients were recruited at the 6 sites. Due to loss to follow up (6) and withdrawals (17) the final sample was 182. There was adequate sample size at 3 out of 6 sentinel sites.

Three sites had the adequate sample size namely Tokombia, Tesseney and Goluj. The other three sites were not able to recruit the required sample size (Table 1).

Table 1 Patients screened and enrolled for the study

Sentinel site	Screened	Enrolled	Severe disease
Sawa	101	13	-
Engela	10	10	-
Tokombia	Not known	60	-
Dubarwa	29	1	-
Tesseney	1,103	52	-
Goluj	142	67	2

Table 2 Patients enrolled on artesunateplus amodiaquine

Sentinel site	Enrolled	ETF	LCF	LPF	ACPR	Total analyzed	Loss	With	% ACPR
Engela	10	-	-	-	9	9	1	-	100
Goluj	67	-	2	-	64	66	1	-	97.0
Tokombia	60	-	2	6	48	56	3	1	85.7

Only Goluj and Tokombia had adequate sample sizes for AS+AQ. Discarding the results from Engela, and analyzing only from Goluj and Tokombia, the aggregated data for AS+AQ: the ACPR was (112/122) 91.8% and total failure (10/122) was 8.2%.

For CQ + SP efficacy study, only Tesseney had adequate sample size. The ACPR for this study site was (22/51) 43.1% and total failure was at (29/51) 56.8% (Table3).

Table 3 Patients enrolled on chloroquine plus sulfadoxine/ pyrimethamine

Site	Enrolled	ETF	LCF	LPF	ACPR	Total analyzed	Loss	With	% ACPR
Dubarwa	1	-	1	-	-	1	-	-	0
Tesseney	52	3	6	20	22	51	1	-	43.1
Sawa	13	1	1	1	10	13	-	-	76.9

ACPR for artesunate plus amodiaquine was (112/116) 96.6% and total treatment failure was (4/116) 3.4%.

Table 4 Patients enrolled on artesunate plus amodiaquine sites with PCR correction

Site	Enrolled	ETF	LCF	LPF	ACPR	Total analyzed	Loss	With	% ACPR
Goluj	67	-	1	-	64	65	1	1	98.5
Tokombia	60	-	1	2	48	51	3	8	94.1
Total	127	-	2	2	112	116	4	9	96.6

The ACPR for CQ+SP with PCR correction was 50% (22/44) and total treatment failure at 50% (22/44).

Table 5 Chloroquine plus sulfadoxine/ pyrimethamine site with PCR correction

Site	Enrolled	ETF	LCF	LPF	ACPR	Total analyzed	Loss	With	% ACPR
Tesseney	52	3	4	15	22	44	1	7	50

Discussion

The NMCP conducted an efficacy study to evaluate the effectiveness of the existing first line drug combination for malaria treatment in Eritrea following reported clinical failures. Patients were recruited from sentinel sites and enrolled in two groups; one receiving chloroquine plus SP and the other receiving artesunate and amodiaquine. The failure rate was assessed clinically, parasitologically and by PCR to correct for possible re-infection during the 28 day study period. The key finding was an unacceptably high failure rate of 50% from chloroquine plus sulfadoxine/pyrimethamine compared to less than 4% for artesunate and amodiaquine.

Malaria treatment failure in this study was determined at three levels; clinically, parasitologically and corrected for using PCR to verify that there was no confounding influence from re-infection. The observed failure rate is therefore authentic. Drug resistance is a major cause of morbidity and mortality from malaria that necessitates consideration of drug treatment regimen change[4]. A drug resistance rate of 10% or greater is high enough to consider drug change. In our study the drug resistance rate confirmed in one study site exceeded the threshold set by the WHO to justify immediate drug treatment change.

One major concern of using the artesunate plus amodiaquine is the cost of the treatment and short shelf life[7]. It has been estimated that the cost of the new treatment is at least ten times that of the current first line treatment even though prices are expected to decrease. In Eritrea, it is still acceptable and feasible to sustain the cost because of the drastic reduction in the malaria disease burden from being the leading killer disease in 1999 to the being out of the top ten killer diseases in the country.

Following the successful achievements of the national and regional Abuja targets for malaria control, the MOH is now targeting the elimination of malaria which would make the introduction of the artesunate plus amodiaquine an important strategic tool to realize this national goal, notwithstanding the threat from importation of the disease from the neighboring countries where the disease is still highly prevalent [8].

These results for chloroquine plus sulfadoxine/pyrimethamine efficacy were therefore a very strong justification for the immediate review with view to change treatment policy from sulfadoxine/pyrimethamine plus chloroquine and incorporation of safe and efficacious ACT. Due to the fact that artesunate plus amodiaquine demonstrated optimal efficacy without any report of side effects, this regimen can be implemented as interim policy for the next malaria transmission season.

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