Efficacy Of Artesunate Plus Cotrimoxazole And Artesunate-Pyrimethamine-Sulphadoxine Combination In The Treatment Of Plasmodium Falciparum Hyperparasitaemia

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SUMMARY

Objective: To evaluate the efficacy of artesunate plus cotrimoxazole and artesunate-pyrimetyhamine-sulphadoxine combination in the treatment of Plasmodium falciparum hyperparasitaemia.

Methods: Fifty children with symptoms compartible with acute uncomplicated Plasmodium falciparum hyperparasitaemia were randomized to receive combination of artesunate with cotrimoxazole or pyrimethamine-sulphadoxine. The children were clinically and parasitologically assessed daily for 8 days and on day 14.

Results: Forty-five children 24 of who were given artesunate plus cotrimoxazole combaination, completed the study per protocol and were evaluated. They were aged between 10 months and 7 years with a mean age of 2.93 ± 1.79 versus 3.75 ± 2.39 years respectively, in the artesunate plus cotrimoxazole (ASCOT) and artesunate-pyrimethamine-sulphadoxine (ASSP) groups. The geometric means of asexual forms of parasite per microlitre were respectively, 409,260 and 324,339 for ASCOT and ASSP. The mean fever clearance time (days) was similar in the two groups 1.33 + 0.52 versus 1.25 + 0.46; p>0.05 and mean parasite clearance was 2.33 days in the two groups. Cure rate on day 14 was 100% for the two groups and both drugs were well tolerated.

Conclusion: We concluded that both treatment regimens are safe and equally effective in the treatment of Plasmodium falciparum hyper-parasitaemia in the study patients.

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IINTRODUCTION

Hyperparsitaemia is said to occur when more than 5% of red cells of an individual is infected and this approximates to parasite density of 250,000 per microlitre of blood in a thick smear [1,2]. In Nigeria, cases of hyperparasitaemia often passed for any other acute uncomplicated malaria and have been treated with commonly available antimalarial drugs including chloroquine, pyrimethamine-suphadoxine, halofantrine, chloroquine plus chlorpheramine or cotrimoxazole [3,4,5]. The apparent lack of specific guidelines for the treatment of this potentially deleterious form of malarial presentation may be due partly to inadequate diagnostic tools and reports of hyperarasitaemia not been an indicator of severity in malaria [6]. Hyperparasitaemia may not be an indictor of severe malaria though, it may predispose to complications including severe anaemia and cerebral malaria. It may be logical to presume that heavy parasite load in an individual will negatively affect viable red cell mass amongst other possibility. Therefore where possible the parasite biomass should be rapidly reduced to forestall any unpalatable consequences.

One veritable means of combating the scourge of malaria in most sub-Saharan African countries is prompt treatment of cases. Artemisinin derivatives are the fastest acting schizonticidal drugs known to date [7]. Apart from cost of this group of drugs, fear of development and spread of resistant strains of Plasmodium falciparum has been expressed by researchers. Combination chemotherapy has been suggested for the treatment of Plasmodium falciparum malaria as a means to prevent or delay the development and spread of resistance with the overall goal of reducing malaria morbidity and mortality [6-10]. Pyrimethmine-sulphadoxine provides schizonticidal effects for several days after a single dose thus making it a convenient treatment option in Plasmodium falciparum malaria. Cotrimoxazole is an effective antimalarial drug with comparable efficacy to that of pyrimethamine-sulphadoxine in the treatment of acute uncomplicated Plasmodium falciparum in children [5,11-13]. We report the efficacy of artesunate plus cotrimoxazole and artesunate-pyrimethamine-suphadoxine in the treatment of Plasmodium falciparum hyperparsitaemia in children suffering from otherwise acute uncomplicated malaria.

PATIENTS AND METHODS

Patients

Fifty children who presented at the General Outpatient Department of the University College Hospital, Ibadan, Nigeria with clinical features suggestive of acute uncomplicated falciparum malaria but with parasite count greater than 250000 were enrolled into the study between May 2003 and March 2004. They were treated on outpatient basis. Other criteria for inclusion were history or presence of fever, absence of concomitant illness consent of parent or guardian. Children with signs of encephalopathy, haematocrit < 20% or inability to tolerate oral medication were excluded from the study.

Prior to enrolment, a careful history was obtained from an accompanying parent or guardian and physical examination was performed. Body weight, height and axillary temperature

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were recorded and thick and thin blood films were obtained for parasite identification and quantification.

Drug treatment

The Children were randomized to receive either two-treatment regimen as follows:

ASCOT group: *Artesunate at a close of 4mg per kilogram body weight on day 0, and 2 mg per kilogram body weight on days 1 and 2, plus cotrimoxazole at a dose of 20 mg of sulphamethoxazole component per kilogram body weight twice daily for 3 days.*

ASSP group: *Artesunate as above plus pyrimethamine-sulphadoxine as a single dose at an approximate dose of 25 mg of sulphadoxine component per kilogram body weight.*

All drugs were administered orally and in tablet form by the study nurse or the attending physician and the children were observed for at least 3 hours in order to ensure that the drug was not vomited. The evening medication was administered by parent or guardian who had been given appropriate instructions. Each parent or guardian gave an account of drug administration at home each time the child was seen for follow-up to ensure that drugs had been properly administered and were tolerated.

Evaluation of response

Clinical observations were recorded daily for 8 days (days 0 - 7) and on day 14. Thick blood films for parasitaemia assessment were prepared at the same time as clinical observations. At each visit, the guardian or parent (and when possible, the child) were interviewed and the child examined for the presence of adverse reactions to the drugs. The antipyretic agent paracetamol, 10 – 15mg/kg of body weight every 8 hours for 36 hours, was routinely given to the patients. Fanning and tepid sponging were also done when necessary.

Giemsa stained blood films were examined by light microscopy under an oil immersion objective at x1000 magnification. Parasitaemia in thick films was estimated by counting parasites relative to leucocytes; 500 sexual forms of *P. falciparum*, or the number of such parasites corresponding to 200 leucocytes, were counted, whichever occurred first. The parasite density was calculated by assuming a leukocyte count of 60000/uL of blood [2]. The parasite clearance time was defined as the time from drum administration until there was no patent peripheral parasitaemia.

The fever clearance time was defined as the time from drug administration until the body temperature fell to 37.4°C or below and remained so for at least 72 hours [14]. This definition was necessary because of the routine use of paracetamol during the first 36 hours of treatment. T

The symptom clearance time was defined as the time between drug administration and the disappearance of all presenting symptoms. Classification of response to drug treatment was according to World Health Organization criteria [15]. Early treatment failure was defined development of danger signs on days 1 through 3, day 2 parasitaemia higher than day 0 or parasite count on day 3 was greater than 25% of the day 0 value. Late clinical failure was defined as the development of danger signs after day 3 in the presence of parasitaemia or presence parastiaemia and axillary temperature > 37.4 on any day from day 4 to day 14 without previously meeting criteria for early treatment failure. Late parasitological failure was defined as presence of parasitaemia on day 14 and temperature of < 37.5°C. Adequate clinical and parasitological response was defined as absence of parasitaemia on day 14 without meeting any of the criteria of early treatment failure or late clinical or parasitological failure

Statistical analysis

Data were analysed using *Epi-Info* [16] version 6. Data were presented in the text and tables as mean ± standard deviation. Normally distributed continuous data were compared by Student's t test. Data not conforming to normal distribution for example, parasite density was logarithmically transformed and geometric mean calculated. Values of p less than 0.05 were taken as significant.

RESULTS

Social-biological characteristics of presentation

Fifty children satisfied the criteria for inclusion and were enrolled into the study. Of these, five were withdrawn on account of repeated vomiting (3) of medication and the other two took concomitant medication (chloroquine (1) and halofantrine (1) on day 2 of follow up. The 3 children with repeated vomiting were treated with the combination of intramuscular artemether and oral pyrimethamine-sulphadoxine, the other 2 did not require further medication but were also followed up till discharge on day 14.

Twenty-four children, (18 females and 6 males) who were given artesunate plus cotrimoxazole and 21 (11 females and 10 males) on the ASSP regimen completed the study and were evaluated. The children on the ASCOT treatment were aged between 0.8 and 6 years with a mean age of 2.93 ± 1.79 years whereas the ASSP children were aged between 1.17 and 7 years with a mean age of 3.75 ± 2.39 years. Of those treated with ASCOT, two and one of these children were aged 5.2 and 6 years while all the offers were aged less than 5 years. Ten of these children were aged between 10 months and 2 years. In the ASSP group, four children were aged between 5 and 7 years and the remaining 17 children were aged less than 5 years. The mean weight was respectively, 11.21 ± 3.95 versus 13.67 ± 5.20 for the ASCOT and ASSP.

Table 1 shows the presenting symptoms of the children enrolled in the study. History of fever was present in all cases and other presenting symptoms include headache (10/24), vomiting (16/24), abdominal pain (1/24), cough (8/24), anorexia (15/24) and diarrhea (4/24) for the ASCOT and headache (2/21), vomiting (5/21), abdominal pain (2/21), cough (5/21), anorexia (14/21) and diarrhea (3/21) for those treated with ASSP. The mean pulse rate of the children who were given ASCOT and ASSP were respectively, 128 ± 12 and 127 ± 18. Similarly, the mean respiratory rate for the ASCOT and ASSP groups were respectively, 34 ± 6 and 31 ± 8. Sixteen and 16 of the children, respectively presented with hepatomegaly and splenomegaly in the ASCOT group and 15 and 13 respectively, presented with hepathomegaly and splenomagaly in the ASSP group.

Table 1: Presenting Symptoms In 45 Children With Plasmodium Falciparum Hyperparasitamia Treated With Artesunate Plus Cotrimoxazole Or Artesunate-Pyrimethamine-Sulphadoxine.

Symptoms	Artesunate plus A cotrimoxazole n = 24	Artesunate-pyrimethamine-sulphadoxine n = 21	Total n-45
Fever	24	21	45(100%)
Vomiting	16	5	21(46.7%)
Headache	10	2	12(26.7%)
Anorexia	15	14	29(64.4%)
Abdominal pain	1	2	3(6.7%)
Diarrhoea	4	3	7(15.6%)
Cough	8	5	13(28.9%)
Duration of illness (days)*			
mean ± sd	2.83±0.58	2.67±0.82	
range	2–4	2-4	
* p = 0.45			

Table 2: Anthropometric And Parasitological Data At Enrolment Of Children Presenting With Plasmodium Falciparum Hyperparasitaemia.

	Artesunate plus cotrimoxazole n = 24	Artesunate-pyrimethamine-suplhadoxine n = 21	
Sex - F:M	18:6	11:10	
Age (years)			P
mean	2.93±1.79	3.75±2.39	
range	0.80–6	1.17–7	
Weight (kg)			P>0.05
mean	11.21±3.95	13.67±5.20	
range	6–17	8–22.5	
Parasite density (/ul)			
Geometric mean	409260	324339	
range	269153–633870	250200-447713	

At entry, the mean haematocrit was 31.4 ± 3.5% and 30.9 ± 2.9% respectively, for ASCOT and ASSP groups. The clinical characteristics of the five children who were withdrawn were similar. Clinical recovery of the 3 children to the rescue drug was prompt and the 2 who ingested concomitant medication also achieved adequate clinical and parasitological response.

Therapeutic response

The mean fever and other symptoms resolution was achieved at a mean time of 1.25 ± 0.46 in the ASCOT group and 1.33 ± 0.52 days in the ASSP group, (p > 0.05). Twnety and 15 of the children on ASCOT and ASSP respectively, had cleared fever within 24 hours of commencement of treatment and by day 2 all had achieved temperature of 37.4°C or less. Anthropometric and parasitological characteristics of the children are shown in Table 2. The pre-enrolment geometric means parasite density were respectively, 409260 and 324339 for ASCOT and ASSP. The means parasite clearance time were 2.33 ± 0.98 versus 2.33 ± 0.52 days respectively, for ASCOT and ASSP. By day 1, four and 0 respectively, of the children on ASCOT and ASSP had cleared parasitaemia but by day 2, 18/24 (75%) and 16/21 (76.2%) respectively, had cleared parasitaemia. All the 24 and 21 children respectively, on ASCOT and ASSP achieved total clearance of peripheral parasitaemia and remained aparasitaemic for the 14 day follow up period.

Table 3: Response Of Children With Plasmodium Hyperparasitaemia Treated With Artesunate Plus Cotrimoxazole Or Artesunate-Pyrimethamine-Sulphadoxine

	Artesunate plus Cotrimoxazole	Artesunate-pyrimethamine-sulphadoxine	
FCT (days)			
mean	1.25±0.46	1.33±0.52	P=0.59
range	1-2	1-2	
PCT (days)			
mean	2.33±0.98	2.33±0.52	**
range	1-4	2 - 3	
Classification of response (%)			
Early treatment failure	0	0	
Late Clinical failure	0	0	
Late parasitological failure	0	0	
Adequate clinical and Parasitological response	100	100	

FCT =Fever clearance time, PCT=Parasite clearance time, **** Equal means**

DISCUSSION

Chemotherapy is undergoing review in most parts of the World and the trend is towards the use combination chemotherapy in particular, artemisinin based therapy [8-10]. Artemisinin derivatives are effective in the treatment of acute uncomplicated, severe or complicated malaria and has also demonstrated efficacy in drug resistant malaria. In this study, all the children were clinically stable though had hyperparasitaemia. Therapeutic response was assessed over 14 day period because after 14 days re-infection is very common in areas of high transmission [2,15] like South-west Nigeria. The children in both treatment regimens were similar in social-biological characteristics. Adequate clinical and parasitological response was achieved in all the children.

In 1989/90, an evaluation of oral medication for hyperparasitamic children carried out in the same study area employed such drugs like chloroquine, amodiaquine mefloquine and pyrimethamine-sulphadoxine. All the drugs were uniformly effective achieving 100% cure rate. It is interesting to note that yet similar evaluation done in 1995 through 2000 in the same area with oral medication including chloroquine, pyrimethamine-sulphadoxine, co-trimoxazole and halofantrine recorded abysmal results of about 40% cure rate [3,6]. The poor response from the latter study coincided with periods of increased level of resistance to chloroquine and pyrimethamine-sulphadoxine in the South-west Nigeria [17-22].

Malaria of all grades of severity should be treated promptly though, it is more imperative when there is hyperparasitaemia. It is logical to expect that hyperparasitaemia will predispose to severe or complicated malaria especially severe anaemia but the extent remains to be determined. It is a recognized fact that in Nigeria most cases of malaria are diagnosed without recourse to microscopy thus making it impossible to determine the level of parasitaemia. Perhaps, this further reinforces the need to make microscopy facility available at all peripheral health centers. Hitherto, parenteral therapy with or without exchange blood transfusion were employed once hyperparastiamia was diagnosed in the non-immune patients [23,24]. The potential dangers inherent in such radical treatment modality and few reports of successful treatment of hyperparasitaemic children with oral medication had since informed modifications. The availability of rapidly schizonticidal drugs like artemisinin derivatives may further enhance the use of oral medication for the treatment of otherwise acute uncomplicated *Plasmodium falciparum* hyperparasitaemia. The use of less rapidly schizonticidal drugs like chloroquine and sulphadoxine-pyrimethamine might negatively impart on the outcome of such episode of malaria and should be discouraged. The present exercise may therefore indirectly translate to making case for deployment of artemisinin based combination chemotherapy for malaria. Further studies will certainly be needed to firmly make such conclusion.

The need to protect/delay development of widespread resistance to artesunate informs the call for combination chemotherapy in malaria. Apart from pharmacological consideration there is need to ensure that combination drugs are simple to administer. Single dose regimen of pyrimethamine-suiphadoxine provides a simple regimen and is therefore attractive. Cotrimoxazole is easily available, affordable and has thorapeutic application vaired microbial diseases. It is worthy of note that respiratory tract infections is common amongst children in the sub-Saharan Africa and sometimes co-exists with malaria. In such instances cotrimoxazole had been prescribed with other antimalarial drugs. Perhaps, the relatively slow

evolution of drug resistant *Plasmodium falciparum* might have been partly due to surreptitious use of combination chemotherapy.

In conclusion, artesunate based combination showed adequate clinical and parasitological response in children who had *Plasmodium falciparum* hyperparasitaemia. Both regimens were also well tolerated in the small group of children enrolled into this study.

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