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Comparative Study of Efficacy of Amodiaquine-Cotrimoxazole and Amodiaquine-Pyrimethamine-Sulphadoxine in the Treatment of Malaria in Nigerian Children

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The objective of the study was to evaluate the tolerability and efficacy of cotrimoxazole plus amodiaquine (aqct) in the treatment of *Plasmodium falciparum* malaria and to compare efficacy of this combination with that of pyrimethamine-sulphadoxine plus amodiaquine (aqsp) in an area of high malaria transmission. Children aged between 6 months and 10 years with clinical and parasitological evidence of *Plasmodium falciparum* malaria were randomized to receive either of cotrimoxazole plus amodiaquine or pyrimethamine-sulphadoxine plus amodiaquine. Ninety seven children (51 and 46, respectively, in the cotrimoxazole plus amodiaquine group and pyrimethamine-sulphadoxine plus amodiaquine group) completed the study per protocol and were evaluated. Pre treatment clinical and parasitological parameters were similar in the 2 treatment groups. The time to clear fever and other symptoms were similar in the two groups 1.64±0.98 vs 1.47±0.74; $p>0.05$. Parasite clearance times were also similar; 2.41±0.67 vs 2.35±0.60 days, respectively, for aqct and aqsp; $p>0.05$. The cure rates on days 14, 21 and 28 were, respectively, 98, 94 and 87% for aqct and 100, 98 and 89% for aqsp treatment groups. The combination of amodiaquine-cotrimoxazole has potentially negative effect on gametocytogenesis. Both drugs were well tolerated. These results indicate that cotrimoxazole plus amodiaquine has similar efficacy to pyrimethamine-sulphadoxine plus amodiaquine in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in children resident in an endemic area of Southwest Nigeria.

Key words: Malaria, children, cotrimoxazole, chemotherapy, Nigeria

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INTRODUCTION

Malaria accounts for about 25% of all the causes of childhood mortality in sub-Saharan Africa and constitutes both direct and indirect economic burden. Resistance of *Plasmodium falciparum* has since been established to virtually all commonly used antimalarial drugs resulting in efforts at protecting the few effective drugs particularly the artemisinin derivatives (White, 1999; Wernsdorfer, 1991). As part of the strategies for controlling the disease and with a view to delaying resistance to available drugs the World health Organization has recommended the use of combination chemotherapy (WHO, 2001). Artemisinin based combination chemotherapy is the preferred regimen as a result of the rapidity of action but non-artemisin based chemotherapy may be considered especially in the resource poor countries. Hitherto, in Nigeria and most other West African countries pyrimethamine-sulphadoxine has been employed for the treatment of chloroquine-resistant malaria. Cotrimoxazole, a combination of sulphamethoxazole and trimethoprim is a broad spectrum antibacterial agent with proven efficacy in the treatment of *Plasmodium falciparum* malaria (Fehintola *et al*., 2002, 2004) This antimalarial effect is exhibited at the recommended or even reduced dosage required for the treatment of sensitive bacteria infections (Fehintola *et al*., 2002). The mechanism of action of cotrimoxazole and, perhaps resistance of *Plasmodium falciparum* to the drug is similar to that of pyrimethamine-sulphadoxine (Milhous *et al*., 1985). Malaria and bacterial respiratory tract infection do coexist in children and in such instances cotrimoxazole has sometimes been prescribed with chloroquine or other common antimalarial drugs (Fehintola *et al*., 2006). One good attraction to the use of cotrimoxazole is the relative ease of administration. It is also easily available and inexpensive. Amodiaquine has been evaluated in combination with sulphadoxine pyrimethamine and its combination with artesunate is one of the recommended drug regimens for the treatment of malaria in Nigeria (Sowunmi, 2002; Anonymous, 2004). We are not aware of any study that has evaluated amodiaquine plus cotrimoxazole in the treatment of malaria in Nigeria, this research is therefore the first from this area. In the present study, we have evaluated the efficacy of amodiaquine plus cotrimoxazole (aqct) in the treatment of falciparum malaria and compared the efficacy with that of amodiaquine-pyrimethamine-sulphadoxine (aqsp). We concluded that aqct is at least, as effective as aqsp in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in the population of children who were treated in this study.

MATERIALS AND METHODS

Patients: One hundred and seven children aged 6 months to 10 years presenting at the out-patient Department of the University College Hospital, Ibadan, Nigeria were randomized to receive cotrimoxazole plus amodiaquine or pyrimethamine-sulphadoxine plus amodiaquine between September and November, 2006. The criteria for inclusion were fever or history of fever in the 24-48 h preceding presentation, pure *P. falciparum* parasitaemia of at least 2000 asexual forms per μL of blood, no antimalarial drug administration in the 2 weeks preceding presentation, absence of concomitant illness and consent of parents or guardians. Children with history suggestive of sickle cell anaemia, haematocrit of less than 20% and those with history of intolerance to sulphonamides were excluded from the study. Withdrawal criteria included: development of concomitant illness, withdrawal of consent or violation of study protocol as approved by the local ethics committee. The study protocol was approved by the Ethics Committee of the Ministry of Health, Ibadan, Nigeria.

Prior to enrolment, a careful history was obtained from an accompanying parent or guardian and physical examination was performed. Body weight and axillary temperature were recorded and thick and thin blood films prepared for parasite identification and quantification. Samples were also collected into capillary tubes for determination of haematocrit and two drops spotted on filter paper for molecular characterization.

Drug treatment and follow up: The children were randomly allocated to receive start dose of pyrimethamine-sulphadoxine at an equivalent dose of 25 mg kg^{-1} of body weight of sulphadoxine component or cotrimoxazole at an equivalent dose of 20 mg kg^{-1} of body weight of sulphamethoxazole component twice daily for 3 days. All the children received standard dose of amodiaquine, that is, 10 mg kg^{-1} body weight as single daily doses for 3 days. All drugs were administered orally and in tablet form (tablets were crushed and mixed with water in the case of very young children), pyrimethamine-sulphadoxine, daily doses of amodiaquine and the first daily doses of cotrmoxazole were administered by study nurse and each child was observed for at least 2 h in order to ensure that the drug was not vomited, if it was, the child was withdrawn from the study. The evening dose of cotrimoxazole was administered by the parent or guardian. Each parent or guardian gave an account of drug administration at home each time the child was seen for follow-up to ensure that the drug had been properly administered.

Evaluation of response: Clinical observations were recorded daily for 5 days (days 0-4), on days 7, 14, 21 and 28. Thick and thin blood films for parasite quantification were prepared at the same time as clinical observations. A repeat sample was taken for assessment of haematocrit on days 7, 14 and 28. At each visit, the guardians or parents and, when possible the children were interviewed and the children examined for evidence of adverse reactions to the drugs. Children with high temperature were given paracetamol, exposed to fan and tepid-sponged when necessary.

Giemsa stained blood films were examined by light microscopy under an oil immersion objective at X1000 magnification. Asexual parasitaemia in thick films was estimated by counting asexual forms relative to leucocytes, 500 asexual forms of *P. falciparum*, or the number of such parasites corresponding to 500 leucocytes, were counted, whichever occurred first. The sexual forms of the parasite were determined by counting micro-gametocytes and macro-gametocytes corresponding to 1000 leukocytes. The parasite density was subsequently calculated by assuming a leukocyte count of 6000 μL^{-1} of blood (Number of parasites/Number of leukocytes multiplied by 6000). The parasite clearance time was defined as the time from drug administration until there was no patent asexual parasitaemia. The fever clearance time was defined as the time from drug administration until the axillary temperature fell to 37.4°C or below and remained so for at least 72 h. This definition was necessary because of the routine use of paracetamol during the first 2 days of treatment. The symptom clearance time was defined as the time between drug administration and the disappearance of all presenting symptoms.

All symptoms and signs emerging after commencement of treatment and/or presenting symptoms and signs that became worse following commencement of treatment were classified as adverse events. Treatment was considered a failure if (asexual) parasitaemia on day 3 was greater than 25% of the day 0 value, if parasitaemia did not clear by day 7 or if parasitaemia cleared before day 7 but reappeared before day 14. The cure rate was defined as the proportion of patients who remained free of parasitaemia on days 14, 21 and/or day 28 of follow-up.

Re-treatment of drug treatment failures: All treatment failures were re-treated with standard regimen of artesunate amodiaquine (Anonymous, 2004) on days 14, 21 or 28 provided they were not symptomatic before this time. None of the children required treatment on account of deteriorating clinical or parasitological condition.

Statistical analysis: Data were analyzed using Epi-Info version 6 (Anonymous, 1994). Proportions were compared by calculating χ^2 with Yates's correction. Normally distributed continuous data were compared by Student's t-test. Data not conforming to normal distribution were compared by the Mann-Whitney U-test or the Kruskal-Wallis test. Values are given in the text and Tables as means±standard deviation (SD); values of $p<0.05$ were taken as statistically significant.

RESULTS

Clinical features at presentation: One hundred and seven children satisfied the criteria for inclusion and were enrolled into the study. Of these, 5 patients received concomitant medication (chloroquine in 3 cases and chloroquine plus erythromycin in 2 cases) thus violating protocol while 5 patients defaulted between days 2 and 4 of follow-up and could not be evaluated. Ninety seven children, (46 females and 51 males) completed the study and were evaluated. Of these, 51 (27 females and 24 males) were treated with amodiaquine-cotrimoxazole and 46 (19 females and 27 males) children were treated with amodiaquine-pyrimethamine-sulphadoxine.

The presenting symptoms were similar in the two groups. All patients had fever and vomiting, was the second commonest symptom found in 67 (69%) of the children. Of the 60 children who were aged less than five years, 41 (68%) had palpably enlarged liver and 24 (40%) of them had splenic enlargement (Table 1).

Clinical response: The mean fever and other symptoms clearance time were similar in the 2 groups: 1.64±0.98 and 1.47±0.74 days, p = 0.34, respectively for amodiaquine-cotrimoxazole (aqct) and amodiquine-pyrimethamine-sulphadoxine (aqsp). Of the 78 children who had elevated temperature documented at enrolment, 42 and 36, respectively, were treated with aqct and aqsp.

Table 1: Various symptoms in patients with acute uncomplicated falciparum malaria

Symptoms	Amodiaquine-cotrimoxazole (n = 51)	Amodiaquine-pyrimethamine-sulphadoxine (n = 46)	Total
Fever	51 (52.6)	46 (47.4)	97 (100%)
Vomiting	37 (38.1)	30 (30.9)	67 (69%)
Headache	14 (14.4)	29 (29.9)	43 (44%)
Abdominal pain	25 (25.8)	21(21.6)	46 (47%)
Diarrhoea	1 (1.0)	1 (1.0)	2 (2%)
Cough	5 (5.1)	8 (8.2)	13 (13%)
Catarrh	6 (6.2)	6 (6.2)	12 (12%)
Duration of illness (days)			
Mean±SD	2.77±1.02	2.63±0.83	
Range	1-7	1-7	

Table 2: Anthropometric and parasitological data at enrolment of children presenting with falciparum malaria

Parameters	Amodiaquine-cotrimoxazole (n =51)	Amodiaquine-pyrimethamine-suplhadoxine (n = 46)	p-value
F:M	27: 24	19:27	
Age (years)			
Mean	4.61±2.46	5.17±2.56	0.27
Range	0.5-10	1-10	
Weight (kg)			
Mean	15.03±5.82	16.15±4.92	0.31
Range	7-39	5-27	
Parasite density (μL^{-1})			
Geometric mean	56493	65464	
Range	4583-1336000	2139-564706	
No. of patients with parasite density >250,000	4 (7.8)	8 (17.4)	
Haematocrit day 0 (%)	27.69±3.99	28.24±3.32	0.46
	20-36	22-38	
Haematocrit day 14 (%)	32.61±2.02	32.58±2.20	0.94
	26-36	21-38	

Table 3: Response of patients with acute falciparum malaria treated with amodiaquine-cotrimoxazole or amodiaquine-pyrimethamine-sulphadoxine

Parameters	Amodiaquine-cotrimoxazole	Amodiaquine-pyrimethamine-sulphadoxine	p-value
FCT (days)			
Mean	1.64±0.98	1.47±0.74	
Range	1-4	1-4	
P : 0.34			
PCT (days)			
Mean	2.41±0.67	2.35±0.60	0.64
Range	1-4	1-4	
Parasitological cure rate (%)			
Day 14	98	100	
Day 21	94	98	0.67
Day 28	87	89	0.75

FCT: Fever Clearance Time; PCT: Parasite Clearance Time

Twenty seven (64.3%) of those treated with aqct and 23 (63.9%) of those treated with aqsp had cleared fever by day 1 and 78.6 and 91.7%, respectively, for aqct and aqsp were afebrile by day 2. Resolution of other symptoms followed similar pattern as fever. Adequate clinical and parasitological response (ACPR) was observed in 98 and 100%, respectively of those treated with aqct and aqsp by day 14. There was no early treatment failure (ETF) but a total of 10 and 6 respectively in aqct and aqsp exhibited late parasitological failure (LPF) mainly between day 21 through day 28 (Table 2 and 3).

Untoward drug effects: In all, 23 patients had documented unwanted effects of the drugs. Of these 8 were treated with aqct while 15 of them received aqsp. Four (8%) and five (11%) children, respectively in the aqct and aqsp groups had mild pruritus. Two and three, respectively, of those treated with aqct and aqsp had nausea and vomiting on day 3 of follow up. Anorexia was documented in 3 patients, 2 of whom received aqct. One and five, respectively, of the children treated with aqsp complained of mild diarrhea and abdominal pain between day 2 and day 3 of follow up. The untoward effects were not severe enough to alter schedule of treatment in these children.

Parasitological response: The enrolment geometric mean parasite density for aqct and aqsp were similar 56493 and 65464 per μL of blood, respectively (Table 2). Table 3 shows the rates of parasite clearance and cure rate for the children. Two (3.9%) and 3 (6.5%) patients who received aqct and aqsp, respectively have cleared (asexual) parasitaemia by day 1. On day 2, 25 (49%) versus 24 (52%) of the children in the aqct and aqsp groups, respectively had cleared their parasitaemia. The parasite clearance time was similar in the two treatment groups, 2.41±0.67 and 2.35±0.60 for aqct and aqsp, respectively (p = 0.64). None of the children in the two treatment groups failed to achieve parasitological clearance by day 4 though, 1, 3 and 6 patients who received aqct and 0, 1 and 5 children treated with aqsp respectively, required to be re-treated by day 14, 21 and 28 of follow up. These patients were treated with standard recommended regimen of artesunate-amodiaquine and were monitored until 14 days after instituting re-treatment.

Gametocytaemia: Gametocytes were detected in peripheral blood in 31 children (31.9%) from both groups (in 15 children at enrolment and in 16 children after initiation of treatment). The overall detection rate at enrolment was 15% (n = 15) and was similar in the two treatment groups, that is 8 (15.7%) and 7 (15.2%), respectively in the aqct and aqsp treatment groups. Following treatment, the emergence of gametocyte was also similar in the two treatment groups; 9 (17.6%) and 7 (15.2%) respectively, for the aqct and aqsp, p = 0.75. The number of patients who were gametocytaemic on days 3, 7 and 14, respectively in the aqct were 3, 2 and 3. On the other hand gametocytaemic patients on days 3, 7 and 14, respectively, in the aqsp group were 5, 3 and 3. Gametocyte sex ratio (male:female) at enrolment was greater than 0 in 2 and 1 patient, respectively, treated with aqct and aqsp. At subsequent follow up, sex ratio of greater than 0 was documented in 4/17 (23.5%) and 5/14 (35.7%), respectively, of those treated with aqct and aqsp during follow up.

Haematocrit: Overall, the mean haematocrit was 28.06±3.54% at enrolment (Table 2). At enrolment the mean haemocrit of those treated with amodiaquine-cotrimoxazole was 27.69±3.99 and was similar to that of aqsp group which was 28.24±3.32. In all the patients haematocrit increased following treatment such that on day 14 the mean haematocrit for the patients were, respectively, 32.61±2.02 and 32.58±2.20 for aqct and aqsp.

DISCUSSION

Cotrimoxazole has been widely used in the treatment of microbial diseases notably bacterial and parasitic infections including *Pneumocystis carinii* and *Plasmodium falciparum*. In Nigeria, cotrimoxazole is often prescribed with commonly used antimalarial drugs once it is suspected that mild bacterial infection co-exists with malaria (Fehintola *et al*., 2006). The effect of this inadvertent use of combination chemotherapy remains to be fully elucidated. While the use of quinoline antimalarial drugs with cotrimoxazole fits the definition of combination therapy in malaria the same will not apply to the use of cotrimoxazole with antifolate antimalarial drugs. In fact such practice would amount to improper drug use. The advantages of artemisinin based combination therapy in malaria remains incontrovertible though, the complete disregard of non-artemisinin based therapy may not serve malaria control programme any good. Therefore, the need to spare no efforts at ensuring the availability of effective malaria therapy in addition to proven efficacy of cotrimoxazole as monotherapy informed this study (Fehintola *et al*., 2002, 2004).

In this study, all the children had symptoms compatible with acute uncomplicated falciparum malaria. Vomiting was the commonest gastrointestinal symptom and it was also the second commonest symptom of malaria in the present study. This observation may be due to relatively high proportion of young children in the study population since vomiting can be easily observed by parents or guardians. The characteristics of the children in the two treatments group were similar and responses to treatment were also comparable. The two regimens had similar fever clearance time and when compared with previous studies involving the use of antifolates as monotherapy the fever clearance time was apparently shorter in the present study (Fehintola, 2004). The fever clearance time observed in this study compares with previous studies in the same area that also employed drug combinations (Sowunmi *et al*., 2005a and b). Parasite (asexual) clearance time and proportion of those clearing parasite by day 2 of follow up were similar in the aqct and aqsp groups and comparable to previous studies in the same area. However, in an earlier study cotrimoxazole monotherapy was observed to have cleared parasitaemia by day 2 in a significantly higher proportion than pyrimethamine-sulphadoxine (Fehintola *et al*., 2004). This observation requires further assessment as it may be rather simplistic to presume unfavorable drug-drug interaction since other measured parameters including parasite clearance time were similar. The cure rates on days 14, 21 and 28 were also similar in the two groups and compares with similar studies in this area.

The documented treatment failures in the study may represent true treatment failures considering that inadequate absorption, individual variations in sulphonamide metabolism have been known to affect the responses to sulphonamide containing drugs. Beyond day 14 in areas of intense malaria transmission as ours, except with the use of molecular markers it may be difficult to differentiate between re-infection and recrudescence. Amodiaquine is common to the two regimens and cotrimoxazole and pyrimethamine-sulphadoxine have similar mechanism of action thus cross resistance would be very likely. However, cotrimoxazole has relatively short half-life and may exhibit lower selection pressure for resistant strains of *Plasmodium falciparum* than pyrimethamine-sulphadoxine. This study did not demonstrate superiority of either of the two combinations employed and treatment outcomes without Polymerase Chain Reaction (PCR) correction were similar and comparable to other regimens in the same area.

High childhood morbidity and mortality in sub Saharan-Africa have largely been accounted for by malaria and respiratory diseases. Combination containing cotrimoxazole may therefore be attractive in instances when malaria coexists with mild respiratory tract infections and such combinations may also be useful in resource poor areas where facilities for diagnosis may be inadequate. It must be duly emphasized that concerted efforts must be made at ensuring provision of adequate facilities at all levels. We posit that population of patients who present with malaria and are suspected or diagnosed to also have mild respiratory tract infections would benefit maximally from regimen containing cotrimoxazole. In that circumstance cotrimoxazole may have to be administered for the standard recommended duration for bacterial infections. On the other hand if respiratory tract infection is not suspected to co-exist with malaria such combinations may not necessarily offer any special advantage but may produce at least similar outcome. However, there is yet the need to confirm these findings and effective studies may also be very important prior to considering it as a policy option. It is noteworthy that the proportion of patients who had gametocytes at presentation was similar in the two groups and consequent gametocyte generation as well as gametocyte sex ratio were similar in the two groups and relatively lower than when either of the antifolate drugs was used as monotherapy (Sowunmi *et al*., 2004, 2005a, b). This observation is presumed to be due to negative effect of amodiaquine on gametocytogenesis as both antifolates particularly pyrimethamine tend to support gametocytogenesis though cotrimoxazole may fair better than pyrimethamine-sulphadoxine

(Sowunmi *et al*., 2004, 2005b). The reduced propensity of cotrimoxazole relative to pyrimethamine-sulphadoxine to support gametocytes may be an added advantage since such will translate to reducing the transmissibility of malaria within the populace.

Cotrimoxazole has been used with encouraging results for the prevention of Pneumocystis Carinii Pneumonia (PCP) in HIV/AIDS patients. Very high dose of the drug is also employed in the treatment of symptomatic Pneumocytis carinii pneumonia although poorly tolerated in majority of HIV/AIDS patients at such doses required to achieve cure. It is also noteworthy that cotrimoxazole also reduces episodes of malaria, respiratory tract infections and diarrhea in people living with HIV/AIDS as well as non-HIV/AIDS individuals (Mermin *et al*., 2004; Thera *et al*., 2005). Intermittent preventive treatment with pyrimethamine-sulphadoxine has been recommended in pregnancy in malaria endemic Africa, it is yet to be determined what role cotrimoxazole will play in the treatment or prophylaxis of malaria and further studies will be required to provide the needed information.

Adverse reactions encountered in the study were, in general, mild and did not necessitate discontinuation of drug treatment in all the children. High doses of cotrimoxazole required for the treatment of PCP are often poorly tolerated but low doses used in this study as well as doses employed for prophylaxis have been well tolerated (Joos *et al*., 1995). Unlike in the previous studies involving cotrimoxazole, none of the children who received cotrimoxazole complained of abdominal pain. However, abdominal pain with or without diarrhea was documented in 5 children treated with amodiaquine-pyrimethamine-sulphadoxine combination. Nine percent of the children had pruritus and might have been caused by the amodiaquine component of the combination.

CONCLUSIONS

Cotrimoxazole in combination with amodiaquine has similar efficacy to amodiaquine plus pyrimethamine-sulphadoxine in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in an area of high malaria transmission of Nigeria. The combination of cotrimoxazole and amodiaquine may also negatively influence gametocyte generation which may be an added advantage. Both drug regimens were well tolerated in the Nigerian children studied.

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