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Efficacy of single-dose amodiaquine co-administered with sulfadoxine/pyrimethamine against falciparum infection in Barkin Ladi, an area of multi-drug resistant malaria

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Abstract

A study was conducted in Barkin Ladi on the North Central plateau of Nigeria to assess the efficacy and tolerability of a single-dose (10 mg/kg) amodiaquine co-administered with sulfadoxine/pyrimethamine (SP) against *Plasmodium falciparum* malaria in children less than 5 years of age using a 14-day protocol. The combination was highly efficacious in 41 patients involved in the trial, producing rapid parasite clearance (MPCR= 2.73 days) and faster clearance of fever (MFCR= 1.2 days). Adequate clinical and parasitological response (ACPR) achieved was 97.6%, while there was 1 (2.4%) case of late parasitological failure (LPF). The single-dose combination produced a significant improvement in PCV ($p<0.05$; $t= 6.390$, $df = 37$), from an average value of 28.7% (±5.2%) on D0 to 34.2% (±3.4%) on D14. The drug combination was well tolerated by the patients; only 2 (4.8%) cases of pruritus occurred amongst the children. The results confirm the efficacy of SP-amodiaquine combination therapy against falciparum malaria.

Keywords: Amodiaquine; Sulfadoxine/Pyrimethamine; Malaria; Nigeria

Introduction

Malaria, caused primarily by *Plasmodium falciparum,* is still a serious health problem in Nigeria. It still is the number one parasitic disease responsible for significant suffering, illness and deaths, most of the burden borne by children under the age of five years and pregnant women. It accounts for 20 – 30% of under-five mortality (FMOH, 2004). Renewed efforts to control the disease in Nigeria started five years ago with the launching of the Roll Back Malaria (RBM) initiative at the Africa Malaria Summit in the national capital, Abuja, in April 2000. Reducing malaria-related mortality in children by improving treatment of cases is one of the primary objectives of RBM in the African Region (Anon., 2001). Contrary to this objective, parasite resistance has continued to worsen against a wide variety of antimalarial drugs used in most countries of sub-Saharan Africa, including Nigeria. In this

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country, studies conducted nationwide in the year 2002 (FMOH, 2002) revealed that chloroquine, hitherto the first line antimalarial drug had lost potency against falciparum malaria parasites: it achieved a mere 43% cure rate in the north central plateau (Molta *et al.*, 2004a). The average adequate clinical and parasitological response from various studies spread across the country was 37.1% ±27.6% (FMOH, 2002).

In the north central plateau, the combination of sulfadoxine/pyrimethamine (SP) produced in 2002; 85% cure rate making it a possible alternative therapy to chloroquine should there be failure with the latter. These observations, replicated in various parts of the country, stressed the need to evaluate alternative therapies for malaria. Recently, the Nigerian Minister for Health inaugurated a high-powered committee to pilot the transition from the old treatment policy to a new policy that involves the use of artemisinin-based combination therapies (ACTs) against malaria. This followed a nationwide trial in 2004 of Artemether/Lumefantrine (Coartem®) and Artesunate/Amodiaquine combinations that demonstrated high efficacy of these products.

Beside the chloroquine and sulfadoxine/pyrimethamine study conducted in 2002, Molta *et al* (2003) assessed the efficacy of amodiaquine monotherapy against uncomplicated *Plasmodium falciparum* malaria on the north central plateau and reported 100% cure rate with this drug. However, the new thrust of malaria treatment involves the use of combination therapies for benefits that include enhanced efficacy and prolonged useful therapeutic life of the component drugs. Therefore, the evaluation of a suitable "partner" drug for amodiaquine was considered imperative (Molta *et al.*, 2003).

This article reports on a study conducted to assess the efficacy of a single dose of amodiaquine co-administered with sulfadoxine/pyrimethamine combination against falciparum malaria in the same area of multi-drug resistance on the north central plateau of Nigeria. This trial was a spin-off from the multi-centre study of ACTs conducted jointly between the Nigerian Federal Ministry of Health (FMOH) and the RBM initiative of the World Health Organization (WHO), Nigeria. It is designed to complement the potential role of the artemisinin-based drugs and to diversify the useful, safe and effective treatment options in the fight against malaria in the country.

Experimental

Study site. This trial of a single dose of amodiaquine co-administered with SP was conducted in Barkin Ladi General Hospital, in an old tin mining district on the north central plateau of Nigeria. Malaria transmission in this part of the country is all-year-round, but demonstrates marked seasonality. *P. falciparum* is the dominant malaria species in the area, accounting for up to 98% of the infections (Molta *et al.*, 2003). Other details about this site are provided in Molta *et al* (2004a, 2004b).

Patient selection and enrolment. Infants and children aged 6 months to 5 years were used in this study. Only those presenting with fever (axillary temperature not less than 37.5°C) qualified for further screening and possible enrolment into the study. Such febrile patients with uncomplicated malaria (pure *P. falciparum* infection) were enrolled. Other selection criteria were as detailed by Molta *et al.* (2004a, 2004b), including parasite density of no less than 1,000 asexual stage parasites per μl (asp/μl) of whole blood, absence of danger signs and willingness to participate in the trial. Parents or guardians provided the required consent prior to enrolment. Unlike the 2002 study, proximity to the hospital was a factor determining eligibility for this trial. On enrolment, patients were administered amodiaquine (Flavoquine® 200mg; Laboratoires Roussel Diamant, 1 Terrasse

Bellini, Cedex, France; Batch/Lot No. 414, Exp. December 2008) at 10 mg/kg together with sulfadoxine/pyrimethamine (Fansidar®, Swipha, Basle, Switzerland; Batch No. 03116, Exp. November 2005) based on age as recommended by the manufacturers.

Evaluation of drug performance. Effectiveness of the treatment was assessed based on parasitological and clinical performance. Changes in parasite loads, axillary body temperatures and other clinical features were monitored on days (D) 1, 2, 3, 7 and 14 and compared against the levels on D0. There was adequate clinical and parasitological response (ACPR) if both fever and parasitaemia cleared completely from the patients by D7 and stayed so to D14. On the other hand, a re-appearance of the parasites with or without fever on D7 or D14 indicated late parasitological failure (LPF). Packed cell volume (PCV) levels were determined on D14 and compared with baseline (D0) values. Trends were examined following descriptive statistics, while paired sample t-test was used to compare mean PCV values of D0 and D14. The methods of Payne (1982) were used to compute the rates of parasite and fever clearance.

Results

A total of 175 infants and children not older than 5 years, were screened for *Plasmodium* infection during this study that evaluated the efficacy and tolerability of single dose treatment of malaria using amodiaquine co-administered with sulfadoxine/pyrimethamine combination in Barkin Ladi, Plateau State of north central Nigeria. Eighty-three (i.e. 47.4%) patients were positive for malarial infection, of which 42 were enrolled. One boy with a low parasite count of 784 asp/μl was dropped from the study. The remaining 41 patients comprised of 19 boys and 22 girls, male: female ratio = 1:1.2. Table 1 presents the demographic data. The average age, weight and height of these patients were 30.7 ± 16.8 months, 12.1 ± 3.7 kg and 83.0 ± 13.6 cm, respectively. All of them were febrile with a baseline mean temperature of 38.2 ± 0.8°C and average PCV value of 28.7 ± 5.2%.

Parasites demonstrated high sensitivity to the treatment (Table 2). The geometric mean densities crushed by 87.9% within 24 hours after the treatment. A 98.8% reduction in parasitaemia by D2. Only 12.2% (5 out of 41) of the patients were still parasitaemic by D3. None of the patients had detectable parasites on D7, but 1 girl aged 20 months had asexual stage parasites in her blood by D14 (density = 278 asp/μl). This was the only case of LPF. All others (97.6%) had ACPR. Crude estimated mean parasite clearance rate (MPCR) is 2.73 days.

Also, the fever cleared rapidly following treatment with the single dose combination (Table 3). By D2, only 1 patient (2.4%) was febrile. This patient had temporary respite on D1. Temperatures were not correlated with parasite densities. Estimated mean fever clearance rate (MFCR) is 1.17 days.

Barely half (46.3%) of the patients had normal PCV values at baseline. The values appreciated in 30 (73.2%), dropped in 4 (9.8%) and remained constant in 4 (9.8%) patients. Blood samples for 3 patients were lost (two spilled and one capillary tube broke during centrifugation). Overall, PCV values showed a significant increase ($p<0.05$; $t=6.390$, $df = 37$) by D14 (34.2 ± 3.4%) over the baseline values (28.7 ± 5.2%). PCV-values were not correlated with parasite densities.

Diarrhoea occurred in only 1 patient; on D1. Also, there was only 1 case of vomiting, again on D1. Pruritus was reported in 2 children, one on D1 and, in the second case on D2 persisting to D3. No other possible adverse reactions were observed or reported. The overall assessment indicated ACPR in 40 (97.6%) of the children and 1(2.4%) LPF.

Table 1: Demographic data.

Parameter	Cases (%)
Number screened	175
Number positive for *Plasmodium* infection	83 (47.4%)
Number enrolled and evaluated	41 (26.1%)
➢ Males	19 (46.3%)
➢ Females	22 (53.7%)
➢ Male: female ratio	1: 1.2
Average age (months)	30.7 ± 16.8
Average weight (kg)	12.1 ± 3.8 (range= 5.5 – 23.0)
Average height (cm)	83.0 ± 13.6 (range= 54 – 115)
Average packed cell volume (D0) (%)	28.7 ± 5.2 (range= 19.0 – 41.0)
Average packed cell volume (D14) (%)	34.2 ± 3.4 (range= 20.0 – 41.0)

Table 2: Changes in *Plasmodium* asexual stage densities following treatment with single dose of amodiaquine co-administered with sulfadoxine/pyrimethamine combination in children.

Day	GMPD (asp/μl)	No. with detectable parasites	Parasite Density Range (asp/μl)
D0	18,217	41 (100%)	1,671 – 106,341
D1	2,199	41 (100%)	80 – 59,556
D2	210	22 (53.7%)	0 – 859
D3	357	4 (9.8%)	0 – 3,104
D7	0	0	0
D14	278	1 (2.4%)	0 – 278

Table 3: Body temperature responses following treatment with single dose of amodiaquine co-administered with sulfadoxine/pyrimethamine combination in children.

Day	Mean temperature (°C)	Temperature range (°C)	No. febrile
D0	38.2 ± 0.8	37.5 – 40.0	41 (100%)
D1	36.7 ± 0.6	35.7 – 38.8	3 (7.3%)
D2	36.5 ± 0.6	35.3 – 38.6	2 (4.9%)
D3	36.5 ± 0.6	35.5 – 38.1	2 (4.9%)
D7	36.7 ± 0.4	35.8 – 37.8	1 (2.4%)
D14	36.6 ± 0.5	35.5 – 37.4	0

Discussion

The findings of this study are useful from several standpoints. First, the study has identified a possible combination drug for amodiaquine for the effective treatment of uncomplicated malaria as suggested by Molta *et al* (2003) following the trial of this drug as monotherapy in this area of multi-drug resistance. The "loading" dose (10 mg/kg) of amodiaquine co-administered with sulfadoxine/pyrimethamine proved effective against the parasites, rapidly clearing fever and parasitaemia as well as improving PCV levels. The combination has a number of the qualities of an "ideal" therapy (Breman *et al.*, 1987), including being widely available and inexpensive (about $2 per adult dose), having few/rare side effects, and capable of being administered orally besides requiring a single-dose.

Parasite clearance with this combination was rapid (average rate = 2.73 days). This is a little shorter than the rate recorded for amodiaquine (3.1 days) as monotherapy (Molta *et al.*, 2003). Also, cure rate increased over the level (85%) achieved with SP alone in 2002 (Molta *et al.*, 2004a). The single case of LPF recorded in this trial is most probably a re-infection, since the patient had no detectable parasites on D3 or D7. However,

this could not be confirmed since "finger-printing" using highly sensitive biomolecular tool was beyond the scope of this study. This is a known drawback of *in vivo* tests that last 10-14 days (Breman *et al.*, 1987).

Mild to near severe anaemia were common among the patients. Barely half (46.3%) of the patients had normal PCV levels at baseline. Bloland *et al* (1993) and Howard and Kuile (1994) draw attention to haematological recovery as indicator of drug treatment performance. It is important that the drug combination brought about significant improvement of PCV values in most patients. Previous study using amodiaquine monotherapy produced insignificant appreciation of PCV (Molta *et al.*, 2003). This confirms the superiority of the combination in achieving haematological recovery.

The single-dose treatment is important from the point of view of the very short elimination half-life of amodiaquine and the much longer half-life of sulfadoxine (81 hours) and that of pyrimethamine (116 hours) (Olliaro and Trigg, 1995). This combines both radical curative and chemoprophylactic advantages. However, prolonged occurrence of drug in the blood is considered to exert selection pressure for resistant parasites, and so could be counter-productive.

To some extent, the present data confirm the report of Deloron *et al* (1988) that the combination of amodiaquine and SP is effective against *P. falciparum* in an area of chloroquine resistance in Rwanda. However, in their study, Deloron *et al* (1988) used a 25 mg/kg regimen of amodiaquine as against the 10 mg/kg employed in this study.

The new malaria treatment policy has artemether/lumefantrine as first line drug. Artesunate/amodiaquine is recommended as alternative. While Nigerians, especially those living in semi-urban and rural communities await the arrival of the new artemisinin-based ACTs, the combination of amodiaquine and sulfadoxine/pyrimethamine that are widely available could provide much needed alternative for the treatment of uncomplicated malaria.

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