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Comparative Assessment of the Clinical Performance of Chloroquine and Sulphadoxine/Pyrimethamine in the Treatment of *Plasmodium Falciparum* Infection in Plateau State: An Open Randomised Study of 109 Children with Acute Uncomplicated Malaria

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Summary

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Background: Malaria remains one of the most common threats to child survival in Nigeria. Chloroquine (CQ) is the first line drug of choice against uncomplicated malaria. In view of reports indicating an increasing resistance of P. falciparum to CQ, a regular surveillance of malaria therapy requires constant evaluation of its efficacy and that of suitable alternatives.

Objective: To compare the current efficacy of CQ with that of sulphadoxine/pyrimethamine (SP) in the treatment of P falciparum infection in Plateau State.

Patients and Methods: Using a 14-day protocol, an open randomized study of the efficacy of CQ and SP in the treatment of uncomplicated P. falciparum infection was conducted in 109 febrile children under five years of age in the Barkin Ladi Local Government Area of Plateau State. Adequate clinical response (ACR), adequate clinical and parasitological response (ACPR) and clinical efficacy (CE) were assessed in the two treatment groups.

Results: Out of the 708 children screened for P. falciparum parasitaemia, 378 (53.4 percent) tested positive. One hundred and nine of the 115 children who qualified for enrollment, completed the study. Fifty-four and 55 children received CQ and SP, respectively. The mean (SD) duration of illness before presentation at the hospital was 1.5 (0.71) days. The means of age, temperature, packed cell volume and parasite counts on admission to the study were similar in the two treatment groups. Thirty-nine (75 percent) of the 52 children who received CQ, and in respect of whom the data was complete, attained clinical cure compared to 52 (94.5 percent) of 55 children on SP ($p = 0.013$). Twenty-seven (51.9 percent) of 52 children treated with CQ versus 48 (87.3 percent) of 55 children on SP achieved adequate clinical and parasitological cure ($p=0.00010$). Thirty (57.7 percent) of 52 children on CQ versus 48 (87.3 percent) of 55 children who received SP were clinically cured ($p = 0.0012$). Failure to achieve fever clearance by day 14 was noted in eight (16.7 percent) of 48 children on CQ against four (7.3 percent) of 55 children on SP.

Conclusion: Although both drugs fell short of a hundred percent cure rate, CQ performed less creditably than SP in the treatment of uncomplicated malaria. There appears to be an urgent need to seek other effective alternative first-line anti-malarial drugs in the country.

Introduction

MALARIA, a major health concern in sub-Saharan Africa, is responsible for considerable morbidity and mortality in children.[1] As one of the commonest causes of under-five mortality in Nigeria,[2] it remains a topical and major issue on the national health planners' agenda. The recommended first line drug for the treatment of uncomplicated malaria in Nigeria is chloroquine (CQ), while sulphadoxine/pyrimethamine (SP) is used as a second line drug in CQ-sensitive areas but as an alternative to first line drug in CQ-resistant areas, or in patients unable to tolerate CQ. This policy is being continuously evaluated, reviewed and updated whenever appropriate, under the National Malarial Control Programme. In Nigeria, chloroquine resistance has continued to increase in prevalence, intensity and geographical spread since the first reports in the 1980s.[3-

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[7] As a result, the performance of this and other commonly used anti-malarial drugs are regularly and frequently monitored through sentinel surveillance and periodic drug efficacy testing (DET).

A cardinal element of the Roll Back Malaria (RBM) initiative is to take evidence-based decisions regarding malaria control measures. In the present study, which is part of nationwide DET effort, the current clinical responses of P. falciparum to CQ and SP in an endemic area in north-central Nigeria were compared. The ultimate aim was to ascertain the continued usefulness or the need to replace these drugs in the treatment of uncomplicated malaria in the area.

Materials and Methods

Study Site

The study was conducted at the general hospital, Barkin Ladi (B/Ladi), about 50 km from Jos, the capital of Plateau State, from August to September 2003. Birkin Ladi is the headquarters of the Barkin Ladi Local Government Area (LGA). The major occupations of the inhabitants are farming and mining activities with the attendant environmental degradation and consequent suitable breeding sites for mosquitoes. The children who were from all the five districts of the LGA namely, Fan, Foron, Gashish, Heipang and Ropp, were recruited through community mobilization. The state owned media (radio and television) and the National Television Authority whose signals are usually received by the people in the LGA, were employed to disseminate information about the study, in order to achieve maximum community mobilization.

Selection Criteria

The procedures used in this study were adopted from the standard World Health Organization protocol (WHO/MALA/96.1077, Geneva: WHO).[8] Children aged six months to five years were screened for malaria parasite infection by microscopic examination of Giemsa-stained thick and thin blood films. Positive cases with a minimum of 2000 and maximum of 250,000 asexual stages per microlitre of P falciparum and who had not taken any anti-malarial drugs in the preceding seven days prior to screening, were enrolled into the study. Drug history was confirmed by a negative Dill Glazko urine test.[9] Other inclusion criteria were mono-infection with *Plasmodium falciparum*, axillary temperature >37.5°C, ability to tolerate oral medication, and ability to attend for follow-up visits for the 14-day protocol period. Informed consent was obtained from the accompanying parent/guardian. The exclusion criteria were the presence of hypersensitivity to sulphonamides,

Table I

Comparison of Admission Features in the Two Groups

Parameters	*Mean (SD)*		*t-test*	*p-value*
	CQ Group	*SP Group*		
Age (months)	3.90 (14.50)	26.56 (14.94)	1.894	0.061
Temp on D0	38.68 (0.98)	38.41 (0.77)	1.624	0.107
PCV on D0	33.17 (5.64)	33.71 (6.06)	0.472	0.637
Parasites count	633833 (452648)	56974 (49245)	1.000	0.322
Male/female ratio	1:1	1.5:1		

PCV = Packed cell volume Temp on D0 = Temperature at recruitment
CQ Group = Chloroquine group; SP group = Sulphadoxine/pyrimethamine group

Table II

Response to Treatment with CQ and SP

Types of Response	*Number of Patients (percent)*		X^2	*p-value*
	CQ group (52)	*SP Group (55)*		
ACR	39 (75)	52 (94.55)	6.57	0.0130
ETF	3 (6.77)	2 (3.64)	0.00	0.6726
LTF	3 (5.77)	0 (0)	1.49	0.1113
ACPR	27 (51.92)	48 (87.27)	14.29	0.0001
CE	30 (57.69)	48 (87.27)	10.39	0.0012

ACR = Adequate clinical response ETF = Early treatment failure LPF = Late treatment failure
ACPR = Adequate clinical and parasitological response CE = Clinical efficacy

Table III

Fever Clearance following Treatment with CQ

Day	*No. of Patients*	*No (%) febrile*	*Mean Temp in °C (SD)*	*Range*
0	54	54 (100)	38.7 (0.98)	37.5 – 40.7
1	53*	16 (30.19)	37.1 (1.07)	35.8 – 39.8
2	54	8 (14.15)	36.9 (0.86)	35.4 – 39.8
3	53*	4 (7.55)	36.8 (0.58)	35.8 – 39.8
4	53*	2 (3.78)	36.7 (0.38)	35.8 – 39.0
7	52*	5 (9.62)	36.7 (0.49)	35.8 – 38.3
14	48*	8 (16.67)	36.8 (0.68)	35.4 – 39.0

* Temperature data not complete

CQ-associated pruritus and the presence of skin ailments that could increase the risk of adverse reactions to the scheduled drug, for example, eczema and pemphigoid exanthemata. Other exclusion criteria were the presence of severe malnutrition, severe anaemia (PCV<15), inability to drink or breastfeed, more than three episodes of vomiting, history of convulsions during the present illness, lethargy or coma, and inability to sit or stand. Patients with acute respiratory infections were also excluded from the study on the ground that such infections might confound the clinical picture of malaria, while others who were taking oral co-trimoxazole or tetracycline eye preparations were excluded because of the anti-malarial activities of these drugs.

On recruitment, each patient's age, weight, height and temperature were recorded. Also recorded were the full names and descriptive addresses of the parents/guardians; these were to enable the research team visit the child if and when they failed to return for follow-up. Laboratory parameters including the parasite count and haematocrit were recorded for each patient on the first day (D0), before commencement of the anti-malarial drug. Parasite count was determined using the formula: Parasitaemia (per μl) = number of parasites x 8000/number of leukocytes. Only patients with haematocrit >15 percent were recruited. The two microscopists who studied the blood films exchanged slides to cross check parasite density counts. Where necessary and as a quality control measure, sessions were held to view and further discuss difficult slides,

Treatment and Course of Illness

Patients were randomized to two treatment groups for the purpose of drug administration and evaluation. One group received chloroquine (*May and Baker Nigeria Plc*, Batch No. 031120709; Mfd.02 2002 and Exp. 02 2007 with NAFDAC Reg. No. 040321) while the second group was given sulphadoxine/pyrimethamine. (*Swiss Pharma Nig. Ltd*, Lagos, Nigeria. Lot No. 22026; Mfd.

Table IV

Fever Clearance following Treatment with SP

Day	*No. of Patients*	*No (%) febrile*	*Mean Temp in °C (SD)*	*Range*
0	55	55 (100)	38.4(0.76)	37.5 – 40.0
1	55	26 (47.27)	37.4(1.11)	35.4 – 40.0
2	55	14 (25.45)	37.2(1.03)	35.8 – 40.0
3	55	2 (3.64)	36.47(0.55)	35.1 – 38.2
4	55	7 (12.73)	36.78(0.87)	34.9 – 40.0
7	55	2 (3.64)	36.75(0.62)	35.0 – 39.4
14	55	4 (7.27)	36.81(0.65)	36.0 – 39.3

03 2002 and Exp. 03 2007 with NAFDAC Reg. No. 040154). Chloroquine was given at a dose of 10mg/kg body weight for the first two days and 5mg/kg on the third day. Sulphadoxine/pyrimethamine was administered as a single dose equivalent to 1.25mg/kg body weight. In respect of SP, parents/guardians were instructed to use tepid sponging during the initial 24 hours to lower body temperatures. In addition, a dose of paracetamol was administered in the clinic to children who had temperatures over 38.5°C. Both chloroquine and SP were administered in tablet forms using the direct observation therapy method; the children were further observed in the clinic for at least, 30 minutes in order to ensure that the drug was not vomited. All patients were thereafter followed on days 1–4, 7 and 14. At the follow-up visits, each patient was assessed for the presence of danger signs, history of fever and medication in the previous 24 hours, while the axillary temperatures were recorded. Thin and thick blood films were obtained for repeat parasite counts. Chloroquine was administered on days 1 (D1) and 2 (D2) as indicated above, to complete the course of treatment, while patients on SP received placebo (vitamin C) to complete the three days of treatment. Reasons for exclusion from the study or loss to follow-up were noted.

An overall classification of the therapeutic response was carefully recorded for each patient as follows: adequate clinical response (ACR), adequate clinical and parasitological response (ACPR), early treatment failure (ETF), late treatment failure (LTF), late parasitological failure (LPF), and clinical efficacy (CE). Early treatment failure was defined by any of the following: (i) development of danger signs or severe malaria on days 1, 2, or 3 in the presence of parasitaemia, (ii) parasitaemia on day 2 higher than the count on the day of admission (D0), irrespective of axillary temperature, (iii) parasitaemia on day 3 with axillary temperature e"37.5°C. (iv) parasitaemia on Day 3 that was e"25 percent of Day 0 count. Late treatment failure (LTF) was defined by any of the following: (i) development of severe malaria after-Day 3 in the presence of parasitaemia without previously meeting any of the criteria of early treatment failure, (ii) presence of parasitaemia and axillary temperature e"37.5°C on any day from D4 to D14, without previously meeting any of the criteria of early treatment failure, (iii) presence of parasitaemia on D14 and axillary temperature <37.5°C without previously meeting any of the criteria of early treatment failure or (iv) late parasitological failure (LPF). Adequate clinical response (ACR) was defined by (i) absence of parasitaemia on D14 irrespective of axillary temperature, (ii) axillary temperature less than 37.5°C irrespective of the presence of parasitaemia without previously meeting any of the early or late treatment failure. Adequate clinical and parasitological response (ACPR) was defined as absence of parasitaemia and pyrexia on D14 without previously meeting any of the criteria for early treatment failure or late parasitological failure. Clinical efficacy (CE) was defined by the combination of late parasitological failure (LPF) plus adequate clinical and parasitological response (ACR).

Alternative treatment was given for drug failures according to standard practice; this was SP or amodiaquine in the case of CQ failure, and quinine in those who responded poorly to SP.

Statistical analysis

Means of continuous variables were compared using Student's t test. Frequencies were compared using chi-squared or Fisher's exact test where appropriate. P-values less than or equal to 0.05 was considered statistically significant.

Results

The blood films were positive for malaria parasites in 378 (53.4 percent) of the 708 children who were screened. Of this number, 115 satisfied the criteria for

enrollment and were therefore recruited into the study. The mean (SD) duration of illness before presentation at the hospital was 1.5 (0.71) days. Six (5.2 percent) of the 115 patients were excluded from further analysis. This number included one patient who developed bloody diarrhoea and was admitted for further investigations and treatment; the mother took another patient to a health facility where alternative anti-malarial was administered, while four others were lost to follow-up and could not be located at the given home addresses. Of the remaining 109 patients that completed the study, 55 received sulphadoxine/pyrimethamine and 54, chloroquine. The mean age, D0 temperature, D0 PCV, D0 parasite counts and the male/female ratios were similar in the two treatment groups (Table I).

When the responses to the two drugs were compared, SP proved superior to CQ. This is indicated by the significant differences in the proportion of patients that achieved adequate clinical response (ACR), adequate clinical and parasitological response (ACPR) and clinical efficacy (CE) between the two treatment groups (X^2 and p-values of 6.57, 0.013; 14.9, 0.0001; and 10.3, 0.0012, respectively – Table II). Fever clearance in response to treatment with CQ and SP is shown in Tables III and IV. By D7, five (9.6 percent) patients who received CQ were still febrile compared to two (3.6 percent) patients on SP. These figures increased on D14 with eight (16.7 percent) in the CQ group compared to four (7.3 percent) in the SP group (Tables III and IV).

Discussion

The threat of malaria remains one of the most serious concerns in Nigeria. The burden of the disease continues to be heavier on children relative to the other groups at risk for malaria, such as pregnant women.[2] More than half of the children screened in the present study had positive blood film for malaria parasites. Previous studies have identified a prevalence of up to 70 percent in various parts of northern Nigeria.[7] Most of the families of the infected children in the present study lived on subsistent agriculture and in an environment degraded by tin mining activities with large craters that act as favourable breeding sites for the vectors of malaria parasites. Such poverty and the ecology have synergistic effect on malaria transmission with increased morbidity and mortality from the disease. It is for these reasons that the monitoring of malaria therapy remains an important component of malaria control programme in this endemic area.

The present study of the performance of CQ and SP in the highlands of central Nigeria demonstrates a significant failure in the efficacy of CQ in the treatment of acute uncomplicated malaria compared to SP, which remains relatively effective against P. falciparum in the area. This finding has serious implication for the control of malaria in this part of Nigeria. Chloroquine is the most extensively used anti-malarial drug in the country. Over the years, it has proven to be the most accessible, even in remote villages and the most affordable. In addition, the drug is produced by various manufacturers, a situation that encourages adulteration. The anti-pyretic effect of CQ confers on it a special advantage that makes it the drug of first choice for the treatment of malaria for many families. If CQ is withdrawn from the essential drug list on account of widespread resistance of P. falciparum, it will be difficult for the Roll Back Malaria programme in Nigeria to find a suitable replacement.

Resistance to CQ in the north-central area of Nigeria portends a substantial problem for the rest of the country. Previously, the worry of malariologists and the Federal Ministry of Health and Human Services used to be the rising incidence of CQ-resistance in the southern parts of the country.[3-5] For example, in a study of children with cerebral malaria, up to 62 percent of the affected children had previously been treated with CQ.[10] Appearance of significant resistance in the northern parts would therefore, indicate that the position of CQ as the first line drug against malaria in the entire country is now threatened. In this period when everyone, especially mothers are being empowered to treat malaria with CQ and the ongoing campaign against malaria by the RBM initiative, it would be difficult to imagine a Nigeria without CQ. The risks of an upsurge in the incidence of severe and complicated malaria, school absenteeism, loss of man hours, and the severe impact all these would have on the Nigerian economy would be enormous.

It is difficult to postulate the mechanism of the emergence of CQ-resistance in the country. Factors that are known to be responsible for resistance of P. falciparum spp. to the 4-aminoquinolines include plasmodial mutation, drug pressure, and decline in the immunity of the human population against malaria.[11] Another factor that promotes plasmodial resistance is the transmigration of human populations. Transporting resistant gametocytes to formerly free areas, or migration of vulnerable subjects to endemic areas will increase resistant mutants. In Nigeria, transmigration of people due to communal clashes, and the volume of business trips between the northern and southern Nigeria and drug pressure, may largely explain the sharp rise in the incidence of resistance to CQ.

The clinical response to SP was better in the present study with ACR, ACPR and CE of 94.55, 87.27 and 87.27 percent, respectively. All the patients with pyrexia between D3 and D14 had parasitaemia. Even though it is a second line drug against P. falciparum malaria, it is widely used in the country especially for patients with

CQ associated pruritus. Nevertheless, resistance to SP has been documented in the southern parts of Nigeria.[12,13]

In conclusion, the present drug efficacy test in the north-central part of Nigeria shows a failure in the clinical performance of both CQ and SP but compared to CQ, SP was more efficacious against P. falciparum malaria. This is perhaps an indication or evidence to support the need to replace CQ as the first line drug of choice in order to enhance the gains of RBM in the country. A combination of SP with amodiaquine, which has previously been shown to be effective against P. falciparum malaria in this area, may augment SP.[14]

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