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Short Report: Comparison of Chlorproguanil-Dapsone with a Combination of Sulfadoxine-Pyrimethamine and Chloroquine in Children with Malaria in Northcentral Nigeria

Oluwagbenga Ogunfowokan, Musa Dankyau, Aboi J. K. Madaki, and Tom D. Thacher*

Department of Family Medicine, Jos University Teaching Hospital, Jos, Plateau State, Nigeria; Department of Family Medicine, Evangelical Church of West Africa Evangel Hospital, Jos, Plateau State, Nigeria; Department of Family Medicine, Mayo Clinic, Rochester, Minnesota

Abstract. Effective and affordable treatment of malaria is critical in the face of resistance of *Plasmodium falciparum* to chloroquine (CQ) and sulfadoxine-pyrimethamine (SP). We conducted a randomized controlled trial comparing the efficacy of chlorproguanil-dapsone (CD) with a combination SP plus CQ in children in Nigeria less than five years of age with malaria. Of 264 children enrolled, 122 (89.7%) and 118 (92.2%) completed the study in the SP + CQ and CD groups, respectively. By day 3, 96 (78.7%) and 94 (79.7%) had cleared their parasitemia ($P = 0.79$), and 107 (87.7%) and 109 (92.4%) were symptom free ($P = 0.32$) in the SP + CQ and CD groups, respectively. Adequate clinical and parasitologic response at day 14 occurred in 111 (94.1%; 95% confidence interval [CI] = 91.6–95.7%) in the CD group and 113 (92.6%; 95% CI = 89.9–94.3%) in the SP + CQ group ($P = 0.85$). SP + CQ and CD had similar antimalarial efficacy and still provide affordable treatment of uncomplicated malaria in northcentral Nigeria.

Plasmodium falciparum resistance to commonly available and affordable anti-malarial drugs such as chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) is increasing in Nigeria.[1–3] Despite a national policy of using artemisinin-based combination therapy (ACT) as the first-line choice in the treatment of uncomplicated malaria,[4] the drug is not accessible to most of those who need it because of its cost. ACT is expensive and use of artemisinin monotherapy has the potential to promote resistance to ACT in Nigeria.[5] Subsidized ACT is supplied erratically and has been unavailable to patients who do not patronize public hospitals. The Nigerian national policy does not allow for the use of other combination therapies when ACT is inaccessible. A multi-center study conducted by the Federal Ministry of Health in 2004 showed that efficacies of ACT range from 82.5% to 100% across the six geopolitical zones in Nigeria.[6] However, the combination of CQ and SP is still useful for treatment of malaria in northcentral Nigeria.[7]

Chlorproguanil-dapsone (CD) (LapDap) is an antifolate combination similar to SP with two exceptions. First, it is rapidly eliminated and exerts less selective pressure for resistance-conferring parasite mutations than SP. Second, it is active against the SP-resistant forms of parasites found in Africa.[8–10] We hypothesized that CD would be more efficacious than SP plus CQ because CD has not been a commonly used anti-malarial combination in Nigeria.

We compared CD with SP plus CQ for the treatment of malaria in children less than five years of age with malaria in a mission hospital in Jos in northcentral Nigeria. The study was conducted between August and November 2005. Malaria is endemic in the region and transmission occurs throughout the year with greater transmission during the rainy season from May to October. This study was reviwed and approved by the Research and Ethics Committee of the Evangelical Church of West Africa Evangel Hospital Jos. Written informed consent was obtained from the participants' caregivers.

The study population was composed of children 6–59 months of age who were brought to the outpatient department of the hospital with a history of fever. Inclusion criteria were 1) an age of 6–59 months, 2) monoinfection with *P. falciparum* with a parasitemia in the range of 1,000–200,000 asexual parasites/μL, and 3) a rectal temperature ≥ 38°C. We excluded those with severe malnutrition, signs of severe and complicated malaria, febrile conditions caused by diseases other than malaria, history of hypersensitivity reactions to sulfonamide, pyrimethamine, dapsone or chlorproguanil, or a history of bleeding disorder or passage of dark urine. On the day of enrollment, the patients were assessed clinically. Hematocrit was determined using a heparinized capillary tube. Parasite density was determined by an experienced microscopist by counting the number of asexual parasites against 200 leukocytes in a thick blood film. Parasite density, expressed as the number of asexual parasites per microliter, was calculated by dividing the number of asexual parasites by the number of leukocytes counted and then multiplying by an assumed leukocyte density of 8,000 leukocytes/μL.[11] If present, gametocytes were counted and their density was calculated.

Subjects were randomized into two treatment groups in blocks of 10 with treatment allocation concealed in sequentially numbered sealed envelopes. One group received chlorproguanil and dapsone, 2 mg and 2.5 mg/kg body weight, respectively, daily for 3 days under direct observation on days 0, 1, and 2. The dose was repeated if vomiting occurred within 30 minutes of administration. The other group received a combination of CQ and SP. CQ was administered at a dose of 10 mg/kg body weight on days 0 and 1 and 5 mg/kg body weight on day 2. SP was administered as a single dose (25 mg and 1.25 mg/kg body weight, respectively) on day 0. The drugs were given under direct observation and were repeated if vomiting occurred within 30 minutes of administration.

The patients were followed-up on days 1, 2, 3, 7, and 14. Malaria smears were prepared, and clinical assessments including history of treatment emergent symptoms, concomitant drugs taken at home, danger signs, physical examination and measurement of temperature were conducted

* Address correspondence to Tom D. Thacher, Department of Family Medicine, Mayo Clinic; 200 First Street SW, Rochester, MN 55905. E-mail: thacher.thomas@mayo.edu

TABLE 1
Characteristics of the two treatment groups at enrollment*

Characteristic	SP plus CQ	CD
Age (months), mean ± SD	29.9 ± 16.2	29.8 ± 15.1
Sex (M/F)	58/64	60/58
Weight (kg), mean ± SD (range)	13.3 ± 3.2 (7–19)	12.9 ± 3.0 (7–20)
Temperature (°C), mean ± SD (range)	39.3 ± 0.8 (38–41)	40.2 ± 0.7 (38–41.5)
Hematocrit (%), mean ± SD (range)	32.7 ± 4.4 (26–59)	33.2 ± 4.0 (22–44)
Asexual parasite density (count/μL), mean (range)	22,564 (1,000–99,900)	40,369 (1,100–99,999)
Previous treatment		
CQ	6	5
SP	1	1
Major clinical features, no. (%)		
Fever	122 (100)	118 (100)
Diarrhea	26 (21.3)	26 (22.0)
Vomiting	43 (35.2)	27 (22.9)
Cough	19 (15.6)	11 (9.3)
Anorexia	30 (24.6)	27 (22.9)
Splenomegaly	23 (18.9)	27 (22.9)

* SP = sulfadoxine-pyrimethamine; CQ = chloroquine; CD = chlorproguanil-dapsone.

at each visit. Hematocrit was determined on days 7 and 14. The primary outcome was adequate clinical and parasitologic response (ACPR).[11]

A sample size of 118 in each group was required to detect a difference of 9% in clinical and parasitologic response between groups with 80% power. Assuming a 10% dropout rate, a sample size of 130 in each group was targeted. Only data from patients with known efficacy endpoints were included in the per protocol analysis.

The proportion of patients responding to each regimen was compared using the chi-square test. Mean values of continuous variables were compared using the *t*-test. All analyses were carried out with Epi Info version 3.3 (Centers for Disease Control and Prevention, Atlanta, GA). A P value < 0.05 was considered significant.

A total of 889 children less than five years of age had fever during the study. Of 302 (34%; 95% confidence interval CI [CI] = 29.5–38.5%) with a positive malaria smear, 264 met the inclusion criteria and were enrolled. Of those enrolled, 240 (90.9%) completed the study. Of those lost to follow-up, 14 (5.3%) were in the SP plus CQ group and 10 (3.8%) were in the CD group. There were no significant differences in clinical or laboratory characteristics between the SP plus CQ group and the CD group (Table 1).

On day 3, five patients (4.2%) in the CD group had *P. falciparum* gametocytes in their blood and none in the SP plus CQ group had gametocytemia ($P = 0.04$). By day 14, gametocytemia was found in 14 (11.9%) in the CD group and 5 (4.1%) in the SP plus CQ group ($P = 0.03$). At the end of the study (Table 2). 113 (92.6%, 95% CI = 89.9–94.3%) in the SP plus CQ group had ACPR compared with 111 (94.1%, 95% CI = 91.6–95.7%) in the CD group ($P = 0.85$). On day 14, the mean ± SD hematocrits in the SP plus CQ (37.6 ± 4.4%) and CD (36.2 ± 4.1%) groups were not significantly different ($P = 0.16$). There was slight increase in the hematocrit in both groups from enrollment to day 14 that was not significant ($P = 0.23$).

TABLE 2
Sensitivity and resistance pattern of SP plus CQ and CD treatment groups*

Overall assessment	SP plus CQ group, no. (%) (n = 122)	CD group, no. (%) (n = 118)	*P*
Adequate clinical and parasitologic response	113 (92.6)	111 (94.1)	0.85
Early treatment failure	2 (1.6)	1 (0.9)	0.97
Late clinical failure	3 (2.5)	2 (1.7)	0.96
Late parasitologic failure	4 (3.3)	4 (3.4)	0.75

* SP = sulfadoxine-pyrimethamine; CQ = chloroquine; CD = chlorproguanil-dapsone.

A multicenter study conducted in five African countries (Gabon, Kenya, Malawi, Nigeria, and Tanzania) reported a similar overall treatment success with CD of 96%.[12] In a previous study in northcentral Nigeria, 87% of the subjects had an adequate clinical response to SP plus CQ on day 14.[7] Our results indicate that SP plus CQ and CD are still useful anti-malarial combination therapies in northcentral Nigeria. However, we failed to find an advantage of CD versus SP plus CQ, as we had postulated.

We found that CD was significantly less effective in clearing gametocytes than SP plus CQ. Ten percent of patients in western Nigeria had gametocytemia 14 days after treatment with SP plus CQ.[13] Neither SP plus CQ or CD could prevent gametocytaemia, and drug pressure probably induced gametocyte formation, a survival strategy for the parasite, facilitating transmission of *P. falciparum*.[14] However, ACT is effective in clearing gametocytes.[15]

One limitation of our study was the inability to differentiate between re-infection and recrudescence of *P. falciparum*, which could affect interpretation of resistance.[16] Final assessment at 14 days is less likely to be confounded by re-infection than at 28 days in an area of intense transmission, but it may underestimate treatment failure rates.

The national policy in Nigeria on first-line treatment of uncomplicated *P. falciparum* malaria supports the use of more expensive and efficacious ACT. Even in the era of ACT, our results showed that anti-malarial drug combinations such as SP plus CQ and CD could still be used in the treatment of uncomplicated malaria in northcentral Nigeria if ACT is unavailable or inaccessible because of its cost.

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Authors' addresses: Oluwagbenga Ogunfowokan, Department of Family Medicine, Evangelical Church of West Africa Evangel Hospital, Jos, Plateau State, Nigeria, and Department of Family Medicine, Jos University Teaching Hospital, PMB 2076, Jos, Plateau State, Nigeria, E-mail: gbengapaul2002@yahoo.com. Musa Dankyau, Evangelical Church of West Africa Evangel Hospital, PMB, 2238, Jos, Plateay State, Nigeria, E-mail: dankyau2@aol.com. Aboi J. K. Madaki, Department of Family Medicine, Jos University Teaching Hospital, PMB 2076, Jos, Nigeria, E-mail: aboikutak@yahoo.com. Tom D. Thacher, Department of Family Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, E-mail: thacher.thomas@mayo.edu.

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