Effects of Pyrimethamine Versus Proguanil in Malarial Chemoprophylaxis in Children with Sick Cell Disease: A Randomized, Placebo-Controlled, Open-Label Study

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ABSTRACT

Background: Malarial chemoprophylaxis is essential for patients with homozygous sickle cell disease (SCD) who live in areas where malaria is endemic. Endemic regions include most sub-Saharan African countries and Southeast Asia.

Objective: This study compared the efficacy and tolerability of pyrimethamine with that of proguanil and placebo in the prevention of malaria and the complications of *Plasmodium falciparum* infection (hepatomegaly, splenomegaly, bone pain crisis, hemolytic crisis) in children with SCD.

Methods: In this single-center, open-label study conducted in Nigeria, children aged 1 to 16 years with SCD were randomly assigned to receive tablets of pyrimethamine (0.5 mg/kg.wk), proguanil (1.5 mg/kg.d), or placebo (vitamin C, 7 mg/kg.d) for 9 months as prophylaxis from February to December (which includes the rainy season), the period of greatest malarial transmission. The clinical and laboratory features of malaria (presence of parasitemia, parasite count and density, hepatomegaly and/or splenomegaly, symptomatic malarial infection [fever, rigors], bone pain crises, and hemolytic crises) were assessed.

Results: A total of 97 patients completed the study (49 boys, 48 girls; mean [SD] age, 7.8 [4.3] years). The pyrimethamine group comprised 36 patients (mean [SD] age, 8.1 [4.3] years; range, 2–16 years); the proguanil group, 32 patients (mean [SD] age, 9.5 [3.7] years; range, 3–16 years); and the placebo group, 29 patients (mean age, 5.9 years; range, 1–14 years). The male:female ratio was 1.1:1 in the pyrimethamine group, 1:1.7 in the proguanil group, and 1.6:1 in the placebo group. Parasitemia was noted in 7 patients (19.4%) in the pyrimethamine group, 6 (18.8%) in the proguanil group, and 7 (24.1%) in the placebo group at the start of the study. *P falciparum* was the only isolate.

The mean parasite density over the 9-month period was significantly lower with proguanil compared with pyrimethamine ($P = 0.045$) and placebo ($P < 0.05$). The incidence of splenomegaly was least with pyrimethamine, but this group had the most patients clinically diagnosed with malaria. Hospitalizations and episodes of bone pain and hemolytic crisis occurred most frequently with placebo. One patient in the placebo group died of septicemia.

Conclusions: Proguanil and pyrimethamine both reduced parasitemia; however, proguanil significantly decreased mean parasite density more effectively than pyrimethamine. Pyrimethamine and proguanil may protect children with SCD from the complications of *P falciparum* infection despite persistent parasitemia. Proguanil may be more useful than pyrimethamine in the prevention of bone pain crises among patients with SCD. (*Curr Ther Res Clin Exp.* 2003; 64:616–625) Copyright © 2003 Excerpta Medica, Inc.

Key words: malarial chemoprophylaxis, pyrimethamine, proguanil, sickle cell disease.

INTRODUCTION

Malarial chemoprophylaxis in homozygous sickle cell disease (SCD) is of utmost importance in regions where malaria is endemic, such as most sub-Saharan African countries and Southeast Asia. Malaria constitutes a major cause of morbidity in these countries, with an incidence of ~100 million cases worldwide each year.¹ It is responsible for ~1.2 million deaths in Africa each year² and for persistent renal complications worldwide.³

SCD poses a major pediatric challenge. In Nigeria alone, 100,000 children are born with this disorder each year compared with 150,000 children in the rest of the world.⁴ The major factor precipitating crisis in children with SCD in Africa is malaria and the complications of *Plasmodium falciparum* infection (hepatomegaly, splenomegaly, bone pain crisis, hemolytic crisis), which can be fatal.⁵ The role of preventive medicine in SCD has been emphasized.⁶ The management of SCD includes prevention and treatment of malaria with affordable, low-technology procedures, such as chemoprophylaxis and bed nets to provide physical protection from mosquito bites.⁷

When choosing chemoprophylactic drugs, parasite resistance, safety profile, compliance, and administration schedule all should be considered. In Nigeria, no gold-standard therapy has been found for malarial prophylaxis in children with SCD. The most widely advocated and available antimalarial prophylactic drug is pyrimethamine. Proguanil is slightly more expensive than pyrimethamine and chloroquine, but all 3 drugs are affordable for most patients/families. According to current policy in Nigeria,⁸ these 3 drugs and mefloquine are appropriate for chemoprophylaxis. At the University of Port Harcourt Teaching Hospital (Port Harcourt, Nigeria), we use pyrimethamine or proguanil in children. Despite this prophylactic treatment, malarial infections occur frequently in children. The

lack of efficacy of pyrimethamine in parasite clearance in pregnant women was confirmed by a study in Ilorin, Nigeria.⁹ No similar study had been done in children, according to a MEDLINE search for articles published from 1989 to 2001 and including the key terms *malaria*, *chemoprophylaxis*, *antimalarial drugs*, *drug resistance*, *sickle cell disease*, *rainy season*, *bednets*, *pyrimethamine*, *proguanil*, *antimalarial immunity*, and *chemotherapy*. A study in Thailand has shown the superiority of proguanil over chloroquine in prophylaxis against *P falciparum* infection.¹⁰

This study compared the efficacy of pyrimethamine with that of proguanil and placebo in the prevention of malaria and the complications of *P falciparum* infection in children with SCD.

PATIENTS AND METHODS

Study Design

This 9-month, randomized, placebo-controlled, open-label study took place at the University of Port Harcourt Teaching Hospital (Port Harcourt, Nigeria) during the months of February to December (which includes the rainy season), the time when malarial transmission is highest.¹¹

Patients

More than 130 children with SCD were enrolled in the SCD registry of the teaching hospital¹² and, as is routine practice in other parts of Nigeria, they receive weekly pyrimethamine or daily proguanil chemoprophylaxis. Children aged 1 to 16 years with SCD (genotype homozygous SCD, hemoglobin SS) whose condition was stable were eligible for the study. Exclusion criteria included a history of allergy or hypersensitivity to either of the 2 study drugs and failure to appear for 2 consecutive follow-up appointments. Pregnant, possibly pregnant, or breast-feeding girls and girls on contraceptive pills were excluded from the study.

Ethical Considerations

The sample size was calculated based on the prevalence of malarial parasitemia in patients with SCD of 22.1%¹³ using the formula pq/SE^2 , where p = prevalence, $q = 100 - p$, and SE (sampling error) = 5. The adequate sample size was calculated to be 68.9 for each group. Long-term (~40 years) survivors of SCD are still relatively rare in our Nigerian environment, and the study was considered of such national importance that we decided that meaningful results could be obtained with relatively smaller numbers (~100) of patients.

The scientific and ethical basis for using a placebo was the study⁹ in Ilorin, Nigeria, which showed a lack of the efficacy of pyrimethamine in pregnant women. Approval for the present study was obtained from the ethics committee of the University of Port Harcourt Teaching Hospital. An interim report was made to the ethics committee after the first month of the trial, and subsequently at 3-month intervals. Each patient's parent or legal guardian provided written informed consent.

Methods

Children were randomly assigned to receive tablets of pyrimethamine* (0.5 mg/kg·wk),¹⁴ proguanil† (1.5 mg/kg·d),¹⁵ or placebo (vitamin C, 7 mg/kg·d) for 9 months. Randomization was achieved by having sequential patients choose 1 envelope from blocks of 6 sealed opaque envelopes (equal allocation). All of the patients were given a curative dose of chloroquine on enrollment, and those with persistent parasitemia were given sulfadoxine-pyrimethamine. Chloroquine and sulfadoxine-pyrimethamine were used because, despite widespread chloroquine resistance in some parts of Nigeria, sensitivity to sulfadoxine-pyrimethamine is high and drug sensitivity to chloroquine is not uncommon in Port Harcourt.

At the beginning of the study (week 0), all patients received a complete physical examination, including assessment of the liver and spleen size by palpation, complete blood cell count, and *P falciparum* parasite count. Parasite count was done on a Giemsa-stained, thick blood film, which was examined with a binocular microscope (Olympus America Inc., New York, New York) with an oil immersion lens. Parasite density was calculated using the formula $P \times 6000/L = C$, where P is the number of parasites counted over 200 leukocytes, L is the number of leukocytes, and C is the total number of parasites per microliter of blood. The blood sample was considered negative if no malarial parasites were seen after the inspection of 100 microscopic fields.

All children were seen at 2-week intervals for 3 months and then monthly for the remainder of the 9-month study period. Treatment response was assessed using clinical examination and parasite density at 2 weeks and 1, 3, 6, and 9 months of treatment. Efficacy was assessed using parasite density; hepatomegaly and/or splenomegaly (palpable spleen >4 cm below the costal margin); morbidity (number of patients experiencing bone pain, hemolytic, and aplastic crises; number of hospitalizations and blood transfusions required); and mortality. *Bone pain crisis* was defined as a recurrent, bilateral pattern of bone pain, often severe and most commonly affecting the juxta-articular portions of the long bones. Bone pain crisis often is precipitated by skin cooling⁴ and improves with warmth, rehydration, and analgesia. Bone pain crisis also includes dactylitis, which often is found in children aged <2 years. *Hemolytic crisis* was defined as the presence of jaundice, anemia, or splenomegaly in the absence of other precipitating causes. *Aplastic crisis* was defined as bone marrow aplasia from malarial infection. The liver and spleen were measured in centimeters using palpation at inspiration. Bone pain crises, hospitalizations, and blood transfusions were assessed as present or absent. The outcome measure—the mean parasite count over the 9-month follow-up period—was calculated. Hemoglobin concentration and morbidity were the secondary end points.

*Trademark: Daraprim® (Glaxo Wellcome UK Ltd., Middlesex, United Kingdom).

†Trademark: Paludrine® (Glaxo Wellcome UK Ltd.).

Two consultant pediatricians and 4 senior registrars in pediatrics made the clinical assessments. A hematologist assisted by 2 laboratory malaria technologists performed blood sampling, parasite counts, and complete blood counts.

Statistical Analysis

The 95% CI was used as the primary statistic. Intergroup differences were determined using the chi-square test with Yates correction when appropriate. The Student *t* test was used to compare 2 sets of data. $P \leq 0.05$ was considered significant. Statistical analysis was performed using Epi Info 2000® (Centers for Disease Control and Prevention, Atlanta, Georgia).

RESULTS

One hundred one patients were enrolled (pyrimethamine group, 36 patients; proguanil group, 35; and placebo group, 30). Subsequently, 3 patients in the proguanil group and 1 patient in the placebo group who frequently failed to appear for follow-up visits were excluded from the study. Thus, a total of 97 patients completed the study (pyrimethamine group, 36 patients [mean [SD] age, 8.1 [4.3] years; range, 2–16 years]; proguanil group, 32 patients [mean [SD] age, 9.5 [3.7] years; range, 3–16 years]; and placebo group, 29 patients [mean age, 5.9 years; range, 1–14 years]). The male:female ratio was 1.1:1 in the pyrimethamine group, 1:1.7 in the proguanil group, and 1.6:1 in the placebo group. The mean (SD) follow-up period was 5.8 (1.9), 6.4 (2.3), and 4.8 (1.1) months among children receiving pyrimethamine, proguanil, and placebo, respectively.

Blood sample assay revealed that 20 children (20.6%) had malarial parasites at week 0 (pyrimethamine group, 7 children [19.4%]; proguanil group, 6 [18.8%]; and placebo group, 7 [24.1%]). No significant differences were found in the prevalence of malarial parasitemia between the 3 groups at any time during the study (Table I).

Table I. Prevalence (no. [%] of patients) of malarial parasitemia, by treatment group.*

Time Point	Pyrimethamine (n = 36)	Proguanil (n = 32)	Placebo (n = 29)	Chi-Square
0 Week	7 (19.4)	6 (18.8)	7 (24.1)	–
2 Weeks	8 (22.2)	5 (15.6)	5 (17.2)	0.4
1 Month	9 (25.0)	5 (15.6)	4 (13.8)	0.4 [†]
3 Months	10 (27.8)	5 (15.6)	3 (10.3)	1.3 [†]
6 Months	14 (38.9)	7 (21.9)	7 (24.1)	2.1
9 Months	7 (19.4)	5 (15.6)	5 (17.2)	0.4

*No significant between-group differences were found.

[†]With Yates correction.

P. falciparum was the only species isolated in any of the blood samples. The mean parasite density and the mean hemoglobin concentration in each group over the follow-up period are shown in Table II. The mean (SE) parasite density was significantly lower with proguanil (22.1 [0.9]/ μ L of blood) compared with pyrimethamine (904.9 [277.5]/ μ L of blood) ($P = 0.045$) and with pyrimethamine compared with placebo (1538.6 [471.9]/ μ L of blood) ($P < 0.05$).

No significant differences in the numbers of sickle-related events were found between the 3 groups (Table III). Episodes of bone pain crisis occurred in 2 patients (5.6%) in the pyrimethamine group, 0 (0.0%) in the proguanil group, and 5 (17.2%) in the placebo group. Similarly, hemolytic crises occurred in 0 patients (0.0%) in the pyrimethamine group, 3 (9.4%) in the proguanil group, and 7 (24.1%) in the placebo group. Significantly more patients receiving proguanil (15 [46.9%]) and placebo (16 [55.2%]) than pyrimethamine (6 [16.7%]) ($P < 0.05$) had splenomegaly in the course of the study. Significantly more patients receiving placebo (8 [27.6%]) than pyrimethamine (0 [0.0%]) or proguanil (3 [9.4%]) required blood transfusions ($P < 0.05$). Among the patients receiving pyrimethamine, 14 (38.9%) were diagnosed with symptomatic malarial infection with fever (body temperature $>37.5^{\circ}\text{C}$) and malarial parasitemia during the study period compared with 5 (15.6%) in the proguanil group and 9 (31.0%) in the placebo group, but these differences were not statistically significant. Patients who received placebo (11 [37.9%]) were hospitalized more frequently than those who received proguanil (5 [15.6%]) or pyrimethamine (2 [5.6%]), but these differences were not statistically significant.

Reasons for hospitalization were as follows: pyrimethamine group: severe malaria with bone pain crises (2 patients [5.6%]); proguanil group: severe malaria with anemia requiring blood transfusion (3 [9.4%]), and cellulitis of the right upper arm and typhoid septicemia (1 [3.1%] each); and placebo group: severe malaria with anemia (3 [10.3%]), dactylitis with anemia and anemia alone (2 [6.9%] each), and bronchopneumonia with anemia, hepatitis, chronic osteomyelitis, and bone pain crisis (1 [3.4%] each). One patient (3.4%) in the

Table II. The mean (SE) parasite density and hemoglobin concentration at 9 months, by treatment group.

Parameter	Normal Value	Pyrimethamine (n = 36)	Proguanil (n = 32)	Placebo (n = 29)
Parasite density, parasites/ μ L of blood	0	904.9 (277.5)*	22.1 (0.9) [†]	1538.6 (471.9)
Hemoglobin, g/dL	10–15	7.6 (0.2)	7.2 (0.3)	6.8 (0.4)

* $P < 0.05$ versus placebo (unpaired Student *t* test).

[†] $P = 0.045$ versus pyrimethamine (unpaired Student *t* test).

Table III. Morbidity and mortality (no. [%] of patients) over the 9-month treatment period, by treatment group.

Morbidity/Mortality	Pyrimethamine (n = 36)	Proguanil (n = 32)	Placebo (n = 29)	Chi-Square
Organ enlargement				
Hepatomegaly	26 (72.2)	23 (71.9)	20 (69.0)	1.1
Splenomegaly	6 (16.7)*	15 (46.9) [†]	16 (55.2)	16.1
SCD-related events				
Symptomatic malarial infection	14 (38.9)	5 (15.6)	9 (31.0)	3.8
Bone pain crisis	2 (5.6)	0 (0.0)	5 (17.2)	1.8
Hemolytic crisis	0 (0.0)	3 (9.4)	7 (24.1)	2.6
Hospitalizations [‡]	2 (5.6)	5 (15.6)	11 (37.9)	3.3
Blood transfusions	0 (0.0)*	3 (9.4) [†]	8 (27.6)	6.6
Deaths	0 (0.0)	0 (0.0)	1 (3.4) [§]	0.3

SCD = sickle cell disease.

* $P < 0.05$ versus proguanil and versus placebo, with Yates correction.

[†] $P < 0.05$ versus placebo, with Yates correction.

[‡]Reasons for hospitalization were as follows: pyrimethamine group: severe malaria with bone pain crises (2 patients [5.6%]); proguanil group: severe malaria with anemia requiring blood transfusion (3 [9.4%]), and cellulitis of the right upper arm and typhoid septicemia (1 [3.1%] each); and placebo group: severe malaria with anemia (3 [10.3%]), dactylitis with anemia and anemia alone (2 [6.9%] each), and bronchopneumonia with anemia, hepatitis, chronic osteomyelitis, and bone pain crisis (1 [3.4%] each).

[§]Cause of death: viral hepatitis and presumed overwhelming septicemia.

placebo group developed viral hepatitis and presumed overwhelming septicemia and subsequently died. No organism was isolated on culture. The drugs were well tolerated and no adverse events were noted.

DISCUSSION

The choice of malarial chemoprophylaxis has remained controversial.^{9,16–18} In this study, proguanil was found to reduce malarial parasitemia (ie, lower mean parasite density) in the patients, as was reported in Thailand.¹⁰

The newer high-technology approaches to preventing SCD (eg, antenatal diagnosis) or to treatment (eg, bone marrow transplantation) are unlikely to be affordable or to have a discernible impact on the population.⁶ Malarial chemoprophylaxis is not advocated routinely for children in areas where malaria is endemic to promote the development of naturally acquired immunity.¹⁹ However, chemoprophylaxis is recommended for children who are immune suppressed and who have SCD to prevent severe forms of malarial infection and sickle cell crises.¹⁹ Attempts to provide suitable vaccines against the various stages of the malarial parasite to date have not been successful.²⁰ The long-term use of chloroquine is not advocated for prophylaxis in children due to the widespread resistance of *P falciparum* to chloroquine^{21,22} and to the possibility

of ocular damage.²³ Although sulfadoxine-pyrimethamine has been tried in some centers,¹³ its long-term use is not recommended by the World Health Organization because of potential serious side effects.²⁴

Lege-Oguntoye et al²¹ noted that pyrimethamine, being a blood schizonticide, may not fully eliminate malarial parasites from the blood, although the clinical manifestations of the acute malarial attacks will be absent. Similar findings have been reported in other studies.¹⁵ In this study, pyrimethamine chemoprophylaxis did not eliminate malarial parasitemia or the clinical symptoms of the disease, which confirms a previous finding in pregnant women in Nigeria.⁹ It is likely that malarial parasites have developed resistance to pyrimethamine, probably because the drug has been used as a sole chemoprophylactic agent in patients with SCD for 40 years.²⁵

The basis of the effect of sickle cell morbidity in the absence of an effect on parasitemia has been a subject of considerable interest. Ogbuokiri¹⁵ postulated that a reduction in the parasite count may be accompanied by clinical improvement, despite the persistence of parasitemia. However, it is known that the degree of parasitemia does not correlate with clinical symptoms in endemic areas. Transient impairment of immunity to malaria with occasional rebound may occur, but 1 trial²⁶ showed good evidence that prophylaxis improves mean hemoglobin levels and reduces severe anemia, the number of clinical malarial attacks, parasite counts, and spleen sizes.

More patients receiving proguanil had hemolytic crises and more required hospitalization and blood transfusions than patients receiving pyrimethamine. Our finding that a significantly larger number of patients receiving proguanil than pyrimethamine and placebo had splenomegaly may have accounted for the hemolytic crises, although malarial infection without splenomegaly may cause hemolysis in patients with or without SCD.²⁷ This finding may mean that proguanil is contraindicated in tropical splenomegaly syndrome, a clinical condition associated with massive splenomegaly in areas where malaria is endemic.²⁴

It is likely that blood transfusion did not have a significant impact on the results of our study. A total of 11 children underwent transfusion during the study. All had hemoglobin levels <5 g/dL, which increased to 5 to 7 g/dL after transfusion. Therefore, the overall effect on hemoglobin levels was not marked. More importantly, however, transfused blood was not screened for malaria and sulfadoxine-pyrimethamine was routinely given to all children after blood transfusion to prevent "transfusion malaria."

Bone pain crisis is the most common complication of SCD in children.⁴ In this study, 5 patients in the placebo group and 2 in the pyrimethamine group had bone pain crises. No episodes of bone pain crisis were reported in patients who received proguanil. The study in Nigeria⁹ showed the lack of efficacy of pyrimethamine in parasite clearance in pregnant women. Our study confirmed this observation in children with SCD. Therefore, proguanil may be more useful in the prevention of bone pain crises among patients with SCD. Although the causes of hospitalizations among the groups varied, the percentage of hospi-

talizations was numerically highest with placebo (pyrimethamine, 5.6%; proguanil, 15.6%; and placebo, 37.9%), although the differences were not significant, suggesting that pyrimethamine may reduce morbidity despite persistent parasitemia (Table III).

CONCLUSIONS

In this study population of children with SCD in Nigeria, proguanil lowered mean parasite density more effectively than pyrimethamine. Proguanil and pyrimethamine both reduced parasitemia. Pyrimethamine and proguanil may protect children with SCD from the complications of *P falciparum* infection despite persistent parasitemia. Proguanil may be more useful than pyrimethamine in preventing bone pain crises among patients with SCD.

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