Efficacy of Sulphadoxine and Pyrimethamine, Doxycycline and their combination in the treatment of chloroquine resistant Falciparum Malaria

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ABSTRACT

Objective: The present in vivo study evaluates the efficacy of sulphadoxine/pyrimethamine, doxycycline and their combination in the treatment of Sudanese patients infected by chloroquine resistant falciparum malaria.

Methods: Febrile patients with positive blood smears of *Plasmodium falciparum* were given chloroquine 25mg-base/kg body weight and followed up for 3 days. Patients with recrudescence due to chloroquine resistance were readmitted for test treatment. Using simple number randomization patients were divided into groups, A, B and C. These were treated with doxycycline, sulphadoxine/pyrimethamine and a combination therapy of sulphadoxine/pyrimethamine plus doxycycline. Doxycycline was initially administered as a single dose of 200mg followed by 100mg daily for 6 days whereas sulphadoxine/pyrimethamine was given as a single dose of sulphadoxine 1500mg and pyrimethamine 75mg. Patients of group C received the combination therapy of sulphadoxine/pyrimethamine and doxycycline. Clinical observations and examination of blood films were carried out for each patient daily for 6 days and thereafter weekly for 4 weeks.

Results: A high level of chloroquine resistance (75%) was documented amongst 280 patients (age 15-53 years) visiting Omdurman Hospital of Endemic Diseases during 1996-1998. The study demonstrated that only 46% and 78% of the patients were cured after 4 days of treatment by doxycycline and sulphadoxine/pyrimethamine. Patients treated with sulphadoxine/pyrimethamine in combination with doxycycline had a cure rate of 90% and 100% after 3-4 days of treatment, a single recrudescent case was detected on day 6. No relapses occurred during the follow up period. All patients were successfully treated by all regimens with the exception of one case treated by doxycycline. All treatments were well tolerated but a few cases had complaints of nausea.

Conclusion: The combination therapy of doxycycline/sulphadoxine/pyrimethamine appeared to be significantly effective in the treatment of patients with chloroquine resistant falciparum malaria without causing any serious side effects. Such a combination regimen has the advantages of being available at a reasonable cost and less prone to development of resistance.

Keywords: Malaria, resistance, sulphadoxine/pyrimethamine, doxycycline.

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Malaria continues to be a major cause of high morbidity and mortality in many developing countries of Africa, where about 75% of the population live at risk in areas of high endemicity.[1,2] In Sudan, about 1.8m/year patients were admitted for treatment of malaria in major hospitals of the

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northern states where the per cent mortality due to this disease was estimated to be 1.5% of the admitted cases.[3-5] Recently, the spread of resistance to chloroquine (CQ), the first line antimalarial drug in Sudan, had been described as a well documented phenomena in central and eastern parts of the country.[3-5] Patients with recrudescent or CQ resistant malaria are currently treated in Sudan by a combination of quinine (10mg/kg body weight) and a single dose of Fansidar (500mg sulphadoxine + 25mg pyrimethamine).[6] However, patients need to be in compliance with quinine regimen for 7 days that mostly requires hospitalization. Several adverse effects are also common during the pace of quinine treatment.[7] For this reason, it has been our interest to search for an alternative combination that can be effective and less troublesome. In fact, several studies have already confirmed the efficacy of combination therapy in treatment of uncomplicated cases of falciparum malaria.[8-13] Nevertheless, the use of combination therapy has been recently advocated as a strategy that can achieve radical treatment and the control of rapidly developing strains of resistant malaria parasites,[14,15] such as Metzger et al[10] who adopted a combination of sulphadoxine-pyrimethamine (S-P) or CQ with clindamycine for treatment of school children infected with resistant malaria in Gabon whereas, combinations of pyremethamine with tetracycline or cotrimoxazole were similarly evaluated by Sheng et al[16] for treatment of CQ resistant malaria in Nigeria. Fansidar combination with mefloquine has been deployed in some areas with CQ resistance in Thailand.[13-14] Conversely, a study conducted by Price et al[17] concluded that a combination of mefloquine and artemsinine had a higher cure rate (97%) of patients with multiple drug resistant malaria when compared with mefloquine monotherapy (55%). In Sudan, such a trend of chemotherapeutic management has not yet been thoroughly investigated. This study, therefore, is an attempt in this direction that essentially evaluates the use of Fansidar and its combination with doxycycline, an antibiotic that has been currently useful in prophylaxis and the treatment of CQ resistant malaria when combined with either quinine or CQ.[18-21]

Methods. Febrile patients visiting the Out Patient Clinic of Omdurman Hospital for Tropical Diseases (University of Khartoum/State Ministry of Health, Sudan) during August 1996-June 1998, were examined. Patients with blood smears indicating positive *Plasmodium falciparum* infection were treated with chloroquine (25mg/kg body weight) and admitted for a follow up of 3 days. Then, only patients who had recrudescence due to falciparum resistant to CQ (RII=marked parasitaemia reduction >75% of that on day zero but no clearance), or (RIII=no marked parasitaemia reduction, <25% of that on day zero). Within 3 days of follow-up were readmitted to be enrolled into the study. Severely ill patients were immediately given a radical treatment of quinine (10mg/kg body weight) followed by a single dose of Fansidar (500mg sulphadoxine + 25mg pyrimethamine) and excluded from the study. The study was based on single-blinding but the objectives and procedures of the study were explained to all patients and their consent was obtained.

Clinical examination. A pretreatment clinical examination for each patient was conducted to provide information on symptoms and signs of the disease (fever, headache, nausea, vomiting, rigor, sweating, convulsions, abdominal pain, splenomegaly, hepatomegaly and so forth).

Treatment and follow up. Patients selected for this study, were divided into 3 groups (A, B & C) using a simple number randomization. Each patient of group A was given a single dose of 200mg doxycycline on day zero, followed by a daily dose of 100mg for 6 days whereas patients of group B were treated by single doses of Fansidar alone (500mg sulphadoxine & 25mg pyrimethamine per tablet). In group C, each patient was given a single dose of Fansidar (500mg sulphadoxine and 25mg pyrimethamine per tablet) plus doxycycline (200mg) that was concurrently administered, followed by a daily treatment with 100mg doxycycline for 6 days. All patients had a light meal prior to drug administration. Clinical observations were conducted for 6 days and then weekly for 4 weeks. Using finger pricks, thick and thin blood smears were examined to determine the level of falciparum parasitemia, hemoglobin and white cell count. Patients with confirmed parasitaemia or impaired clinical improvement within 72 hours of treatment were immediately given quinine (10mg/kg body weight). Quinine was administered every 12 hours as an intravenous infusion in 5% isotonic solution over a period of 2-4 hours. Intravenous medication was continued for 1-2 days and then replaced by oral administration of quinine sulphate for 7 days. Patients who failed to complete the follow up were excluded from the study.

Results. ***Pretreatment examination.*** As shown in Figure 1, a group of 280 febrile patients with *P.falciparum* parasites in their blood smears were admitted to Omdurman Hospital for Tropical Diseases (University of Khartoum/Ministry of Health, Sudan) for clinical examination and treatment by CQ (25mg/kg body weight). On day 3 following admission, 75% of the patients had recrudescence due to resistant falciparum infection (RII or RIII). Examination of blood smears revealed that all specimens had a high level of malaria parasitemia

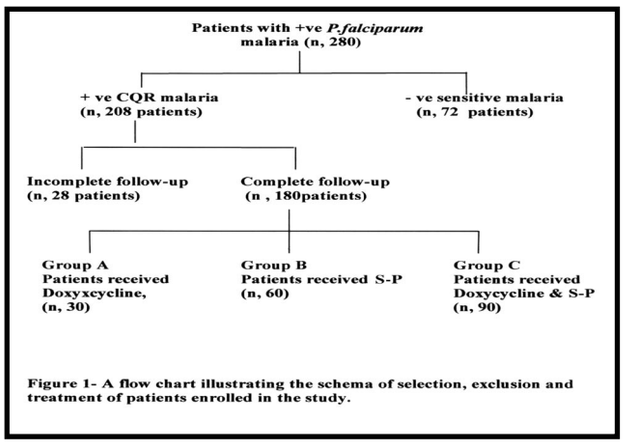

Figure 1 - A flow chart illustrating the schema of selection, exclusion and treatment of patients enrolled in the study.

($5x10^3$-$12x10^3$/ml). Consequently, 208 patients with CQ resistant parasites were readmitted for test treatments as previously described in the methods section. A total number of 180 patients (male/female ratio = 108/72) had been successfully followed up for 28 days but 13.5% (28) failed to complete the study Figure 1. The patients mainly complained of fatigue 95%, fever 90%, nausea 86% and headache 84% whereas 55% had splenomegaly. They had a body temperature of 38-39.5°C, a blood pressure that ranged between 60-100/90-140 mmHg and a normal respiratory rate 20/min. Hematological analysis indicated that the patients had a hemoglobin level >7.5 g/dL and a total white cell count of 3800-8600/ml.

Test treatment and follow up. As illustrated in Figure 2, only 46% of the patients of group A that had been treated with doxycycline, had no parasitaemia in their blood and a significant clinical improvement after 4 days of treatment. In fact, no recrudescence was reported thereafter during the follow up of this group of patients. In group B, the majority of patients (78%) appeared to be cured 4 days after treatment by a single dose of S-P alone. No serious side effects or relapses were reported by any patient of this group following treatment. Interestingly, about 80% of the patients who received S-P in combination with doxycycline had been successfully treated after 72 hours of treatment. On day 4, all patients of this group, n=90 had no parasitemia in their blood smears as illustrated in Figure 2. A single case of recrudescence however, was reported on day 7. Only 2 patients complained of nausea at the beginning of treatment that had been satisfactorily treated using a single dose of phenergan. Chi square analysis revealed that, on day 3 and 4, the combination therapy group had a significantly higher number of cured patients when compared with those of groups A and B treated with S-P and doxycycline, respectively (P<0.001).

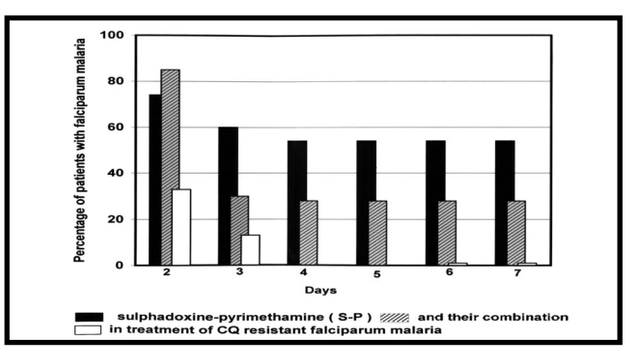

Figure 2 - Efficacy of doxycycline, sulphadoxine-pyrimethamine (S-P) and their combination in treatment of chloroquine (CQ) resistant alciparum malaria.

Discussion. Falciparum CQ resistance had already been confirmed in many parts of eastern and central Sudan[3-5] while the present study provides a new evidence for the occurrence of CQ resistance amongst patients of falciparum malaria visiting Khartoum hospitals (Central Sudan). RI level of CQ resistance was not detected amongst the patients who had a satisfactory response to treatment during the follow-up period (28 days) but only RII & RIII levels of resistance could be confirmed. Essentially, the findings of this study suggest that patients infected by CQ resistant strains of *P.falciparum* parasites can be effectively treated using a combination of S-P (1500mg sulphadoxine & 75mg pyrimethamine) and doxycycline (800mg) whereas S-P and doxycycline appeared to be less effective when administered separately. About 30% of the cases with CQ recrudescence were reported 4 days after treatment with S-P only, Figure 2. Accordingly, the study implied the emergence of some strains of falciparum parasites in the Khartoum area, central Sudan that demonstrated multiple drug resistance in vivo. Multidrug resistance of *P.falciparum* to compounds other than CQ is well documented worldwide but such a phenomenon is not yet thoroughly investigated in Sudan. In a preliminary in vitro study, Khalil[22] recorded that 22% of 27 CQ resistant isolates of *P.falciparum* had demonstrated resistance to one or 2 drugs tested such as CQ, quinine. Babiker et al[5] also noted that parasite clones from eastern Sudan exhibited in vitro as well different levels of resistance to CQ and pyremethamine. The high frequency of resistance to CQ and other antimalarials among parasites in eastern and central parts of the Sudan implies that the extensive use of drugs against *P.falciparum* rapidly selects parasites containing genes of resistance. Alternatively, a genetic aberration may give rise to CQ resistance that also triggers or regulates concomitant expressions of resistance to other distantly related compounds as

previously observed where cross resistance to CQ and other antimalarials such as quinine, mefloquine, amodiaquine was documented.[14,15,21-24] However, this investigation concluded that the antimalarial effect of S-P appeared to be significantly potentiated by the use of doxycycline in treatment of cases with CQ resistant falciparum parasites. A cure rate of 81% and 100% was recorded after 3 and 4 days amongst patients treated with the combination without causing any significant side effects. In fact, patients cured by any of the 3 regimens had no recrudescence for 4 weeks except a single case in group A that received doxycycline only. Such a relapse within a period of 4 weeks in endemic areas of malaria could be related to reinfections. The efficacy of S-P/doxycycline combination could be attributed to the compatible pharmacokinetics of both drugs. Doxycycline has an elimination half life of about 22 hours when the drug is administered as a single dose of 100mg while pyremethamine and sulphadoxine have an elimination half time >90 hours.[6] Unlike other tetracyclines, doxycycline has a better bioavailability and renal clearance.[6]

The study therefore emphasizes the potential role of such an easily administered combination therapy in treatment of non-severe cases of CQ resistance, particularly when the patients cannot afford to be in compliance with quinine treatment for 7 days. However, the findings of this trial need to be furtherly evaluated in a more elaborate field trial, that essentially excludes any bias due to sampling, gender, demographic structure and experience of patients with previous episodes of malaria.

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