

RESEARCH NOTE

PROGUANIL PLUS SULFAMETHOXAZOLE IN THE TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA

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Abstract. In a malaria endemic area of Brazil where *P. falciparum* is highly resistant to chloroquine and Fansidar, we conducted an *in vivo* study to evaluate the therapeutic response of proguanil plus sulfamethoxazole against *Plasmodium falciparum* malaria. Twenty-five adult subjects with uncomplicated *P. falciparum* malaria received supervised drug administration and were followed for 28 days in an inpatient hospital or in a malaria free-transmission area. The therapeutic regimen was proguanil 100 mg BID plus sulfamethoxazole 1,000 mg BID for 7 days. Of those who took all medications (n=21), 17 (81%) were cured. Recrudescence parasitemia during follow-up occurred in four (19%) patients on days 14, 19, 20 and 21 after beginning of treatment. The remaining four (16%) subjects did not complete their therapeutic regimen because of the incidence of side effects. Considering the shortage of falciparum malaria therapeutic options and the urgent need for new regimens to deal with the spread of drug resistant *P. falciparum*, one might consider the study results as a lead to study analogous compounds, hopefully with fewer adverse reactions.

The emergence of resistant *Plasmodium falciparum* strains to chloroquine in almost every endemic areas of the world has resulted in a constant search for new antimalarial drug regimens. Since the 1970's, malaria has become an increasing public health problem in Brazil. In 2000, the Brazilian Ministry of Health reported 610,760 malaria cases, with approximately 20% caused by *P. falciparum* (Ministério da Saúde, 2001). The intense human migration to the Amazon region, the instability of new settlements, and the difficulties in implementing vector control measures have led to an increase of malaria transmission lately (McGreevy *et al*, 1989). Until the end of 70's, Fansidar (sulfadoxine + pyrimethamine) had been used as first line therapy of uncompli-

cated malaria. Unfortunately, resistance to Fansidar developed quickly within a decade, and it can no longer be recommended nowadays (Neifer and Kremsner *et al*, 1991).

Despite the widespread of Fansidar resistance in Southeast Asia, sulfa drugs (sulfisoxazole and sulfamethoxazole) in combination with proguanil in a short term schedule proved to be 95% effective when used as daily malaria prophylaxis (Pang *et al*, 1989). For the chemotherapy of falciparum malaria, studies in Africa have shown promising results for proguanil derivatives combined with sulfa drugs (chlorproguanil plus dapsone for 3 days), although high recrudescence rates are observed when the regimen is limited to a single day (Watkins *et al*, 1988; Amukoye *et al*, 1997). However, studies in Thailand showed poor efficacy of 3-day regimens with either dapsone plus proguanil or dapsone plus chlorproguanil against pyrimethamine-sulfadoxine resistant *P. falciparum* malaria (Wilairatana *et al*, 1997). It has been described that the mechanism of

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Table 1
Distribution of study patients treated with proguanil 100 mg + sulfamethoxazole 1,000 mg every 12 hours for 7 days.

Characteristics	No. (%)
Patients included	27 (100%)
Patients excluded: lost to follow-up (n=1), mixed infection (n=1) ^a	2 (7,4%)
Patients included in the analysis	25 (100%)
Patients who failure: did not tolerate (n=4) ^b , recrudescences (n=4) ^c	8 (32%)
Patients who were cured ^d	17 (68%)

^aOne patient violated the inclusion criteria of 'no mixed infection';

^bSkin rash (n=2) and vomiting (n=2);

^cOne patient violated the inclusion criteria 'no use of antimalarial prior to admission';

^dTwo patients violated the inclusion criteria of 'no travel to endemic area during follow-up' (n=1) and 'baseline level of parasitemia higher than 50,000 parasites/mm³' (n=1)

action of the proguanil plus sulfa combination is similar to that of Fansidar. However, the half-lives of both proguanil and sulfamethoxazole are significantly shorter than for the components of Fansidar (Grose *et al*, 1979; Edstein *et al*, 1990; Newton *et al*, 1993). Recent studies have shown that there may be little cross-resistance between these drug combinations, since the point mutation conferring pyrimethamine resistance is not the same as that one conferring proguanil resistance (Vasconcelos *et al*, 2000). A recent *in vitro* evaluation suggested that, although *in vivo* resistance of Fansidar in the Amazon area is widespread, only 10% of the Amazon strains are resistant to proguanil (Di Santi, personal communication). Therefore, the evidences led us to consider the study of the proguanil plus sulfamethoxazole regimen for the treatment of uncomplicated *P. falciparum* malaria in the Brazilian Amazon area.

The study was designed to test the highest dose compatible with duration of a 7-day therapy. If high cure rate was obtained, a shorter course of therapy (5-day regimen) should be evaluated in further studies. The drug regimen used was proguanil 100 mg plus sulfamethoxazole 1,000 mg every 12 hours for 7 days. In addition, another group of patients was included in a 5-day regimen as a pilot.

Subjects were selected from two sites: the

University Hospital of Cuiabá and the Municipal Hospital of Apiacás, both in Mato Grosso State, Brazil. Although Mato Grosso is a malaria endemic region, there is no malaria transmission in Cuiabá, ruling out the possibility of reinfection. In Apiacás, patients were hospitalized at the local hospital, also free of malaria transmission, for 28 days. After agreement, written informed consents for investigation, treatment and follow-up were obtained from all patients. The study protocol was reviewed and approved by the Hospital Committee for Ethics in Biomedical Research.

Patients who presented at the clinical service of the two hospitals were enrolled in the study if they met the following criteria: uncomplicated *P. falciparum* malaria and parasite density between 500 - 50,000 parasites/mm³ (mixed infections were excluded); age equal or greater than 14 years; no history of antimalarial taken within the past 2 weeks; if women, an indication of the absence of pregnancy; no history of hypersensitivity to sulfonamides; yield to stay in the city for 28 days, and ability to give written informed consent.

On admission, demographic, socio-economic and epidemiologic baseline data (day 1) were obtained. A clinical examination was carried-out on admission and repeated on days 2, 4, 7 and 14. Admission diagnosis was confirmed for all patients by finding asexual forms

of *P. falciparum* in the peripheral blood. Blood examinations were performed on days 1, 4, 7 and 14. Thick blood films were considered negative if no parasites were seen in 100 oil immersion microscopic fields. Otherwise, the number of asexual *P. falciparum* parasites was counted per 200 white blood cells (WBC). Parasite density, expressed as parasites per mm³, was calculated based on the number of parasites per 200 WBC (using 5,000/mm³ as the average density of WBC).

The cure rate was evaluated according to the WHO (1990) criteria for sensitivity (S) and resistance (RI, RII and RIII types) of *P. falciparum* to schizontocidal drugs. Cure (S) was defined as clearance of *P. falciparum* asexual parasitemia within 7 days of treatment initiation, without subsequent recrudescence up to day 28. Since there is no malaria transmission in Cuiabá or within the hospital in Apiacás, reappearance of parasitemia during the 28-day follow-up period after a previous negative result was considered recrudescence, unless the patient reported a trip to an endemic area during the follow-up period. An incident side effect was defined as a sign or symptom arising during the first two weeks of therapy that had not been observed or reported on admission.

The study was analysed using the intention to treat approach. Therefore, "failures" was considered those who could not complete their regimens due to drug side effects or worsening clinical conditions. Patients who left the study ward for non-medical reasons before their 28-day follow-up period were excluded.

Ideally, all patients who did not perfectly fit the study inclusion criteria would be eliminated from analysis. However, for some patients who did violate the study inclusion criteria (noted only after the study was completed), it was possible to be certain about specific study outcomes. These situations were: i) parasitemia at baseline higher than eligibility criteria (if outcome was cure); ii) return to transmission area before 28th-day follow-up period (if outcome was cure); iii) use of prior antimalarials (if outcome was failure). In these cases, if the outcomes were observed in the presence of

such study violation, it was assumed that the same outcome would be observed in the case of no study violation.

Thirty-one subjects were enrolled in the study. Among them 16 were from Apiacás and 15 from Cuiabá. Four were female. The ages varied from 16 to 68 years with a mean (\pm SD) of 35.3 (\pm 13.8) years. The reported number of previous clinical malaria episodes ranged from 0 to 100, with a mean (\pm SD) of 19 (\pm 24.6) episodes. Parasitemias at baseline ranged from 50 to 112,500 parasites/mm³, with a mean (\pm SD) of 9,544 (\pm 21,894) parasites/mm³. Subjects were symptomatic for a mean (\pm SD) of 8.2 (\pm 8.0) days prior to admission (range from 1 to 40 days). A 7-day and a 5-day regimen were administered to 27 and four patients, respectively.

Among the 27 patients who received the 7-day regimen (Table 1), four did not tolerate their medications because skin rash and vomiting (treatment was substituted with mefloquine), 17 were cured, four failed and two were excluded (one was lost to follow-up on day 14 and another was detected with *P. vivax* on day 17 and was treated with chloroquine and primaquine). All patients who failed or could not tolerate the study therapeutic regimen were treated with mefloquine and cleared their parasitemia after 28 days of follow-up.

The mean (\pm SD) parasite clearance times for all 17 patients who were cured was 4.9 (\pm 1.4) days. Among them, two patients traveled into transmission areas after treatment and one of these had the parasitemia above the admission criteria. These two patients were analyzed as protocol violations.

Patients who failed (n=4) had recrudescence parasitemia as follows: one on day 14, one on day 19, one on day 20 and one on day 21. One of these four patients had previous antimalarial therapy identified after enrollment, which was considered a protocol violation.

Using an intention to treat analysis, the cure rate (effectiveness) of the 7-day regimen was 68% (17/25; 95% CI: 47-85%). For only

those who tolerated the 7-day medication course and completed the 28-day follow-up, the cure rate (efficacy) was 81% (17/21; 95% CI: 58-95%). Of the four patients who received the 5-day regimen, three cured and one was lost to follow-up.

The disappointingly high failure rate of this antimalarial regimen was rather unexpected considering the prophylactic success of similar combinations in areas of very high multi-drug resistant *P. falciparum*. This difference may have been due to a causal (rather than suppressive) prophylactic effect (Pang *et al*, 1989). For Africa, previous recommendations have been made to not use drugs as first line therapies when cure rates drop below 85% (Breman and Campbell, 1988). Although our target population is quite different than those of Africa (lower immunity, age, alternative therapies, etc), if one uses this as an overall guideline then our regimen should not be recommended. However, with the urgent need for new regimens to deal with the spread of drug resistant *P. falciparum*, one might consider our study results as a lead to study analogous compounds, hopefully with fewer side effects.

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