MALARIA PROPHYLAXIS WITH PROGUANIL AND SULFISOXAZOLE IN CHILDREN LIVING IN A MALARIA ENDEMIC AREA

by

Lorrin W. Pang, Nipon Limsomwong, Pricha Singharaj, and Craig J. Canfield

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2 The opinions or assertions contained in this paper are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.

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Abstract

The effects of three different daily drug regimens for malaria prophylaxis using either proguanil, sulfisoxazole or proguanil plus sulfisoxazole, as compared to a control group administered vitamins, were studied in 380 children living in a malaria endemic area along the Thai-Burmese border. The subjects, aged 5-16 years, were matched for age, weight and presence of splenomegaly; they were then randomly assigned to receive on a daily basis either proguanil, sulfisoxazole, proguanil plus sulfisoxazole, or vitamins. All medications were administered by the investigators and malaria smears were performed on a weekly basis. Among the 99 subjects taking proguanil plus sulfisoxazole for a total of 1464 man-weeks, there was only one case of falciparum malaria and none of vivax malaria. Statistically, this regimen proved superior to each of the other treatment groups against both Plasmodium falciparum and P. vivax. The data also show that proguanil alone, as a causal or suppressive prophylactic, has poor efficacy against P. falciparum. Side-effects were infrequent and generally mild, except in two subjects whose sulfisoxazole prophylaxis was discontinued because of urticarial rash.

1. INTRODUCTION

During the last three decades, falciparum malaria in Thailand has become increasingly resistant to both treatment (1-7) and chemoprophylaxis (8,9) with multiple drugs, including chloroquine, pyrimethamine/sulfadoxine (Fansidar), and quinine. Because of this multi-drug resistance, the combination of quinine plus tetracycline is generally required to treat falciparum malaria in this country (10). For malaria prophylaxis, two drugs are currently available which have proved to be effective in Thailand. The first drug, mefloquine, is effective when administered weekly (11). The second drug, doxycycline, has recently been shown to be effective when administered daily (12). Neither drug, however, has been used widely for malaria prophylaxis and the long-term tolerance and safety of the drugs are unknown. Recently, a re-evaluation of an older chemoprophylactic, proguanil, has been undertaken. This drug has been used widely and has a long history of safety.

Initially used for both treatment and prophylaxis of falciparum malaria in Asia during the 1940s and 1950s, proguanil soon became ineffective because of the development of drug resistance by both Plasmodium falciparum and P. vivax (13-15). It was felt that the prophylactic failures were suppressive failures, i.e. the inability of proguanil to inhibit the erythrocytic stages, and that the drug might still be effective causally against the exo-erythrocytic stages (16). Compared to other antimalarials, proguanil is relatively free of side-effects. There are virtually no contraindications for its use and it is one of the few antimalarials recommended for use during pregnancy (17,18). Because of its low cost, low toxicity, and recent data suggestive of prophylactic benefit for falciparum malaria (19,20), this drug was tested against Thailand’s multi-drug resistant strains of P. falciparum in an earlier study (21). Compared to a control group given chloroquine, daily proguanil was shown to be a poor prophylactic in Thailand.

In 1973 Black observed in Viet Nam that proguanil, administered at a daily dose of 200 mg, had but a poor prophylactic effect against falciparum malaria, until a sulfonamide, dapsone, was added (22). Since that time, there has developed rapid and widespread resistance of P. falciparum to sulfonamides and other antimalarials, notably
to the pyrimethamine/sulfadoxine drug combination that had been effective in South-East Asia during the mid 1970s (6,7,9). Theoretically, it would not be surprising if present strains showed marked resistance to proguanil plus a sulfonamide since, like pyrimethamine/sulfadoxine, their mechanism of action is considered to be that of a dihydrofolate reductase inhibitor. However, Black's important finding needs to be re-examined in the light of today's highly drug-resistant strains of *P. falciparum* in South-East Asia.

In the present study, it was decided to test proguanil combined with the sulfonamide, sulfisoxazole. The decision to use sulfisoxazole was based on its short half-life, its prophylactic use in children against otitis media (23,24) and meningitis (25,26), and its widespread availability. Furthermore there is evidence that sulfonamides with short half-lives may have less severe side-effects compared to those with longer half-lives, which are thought to be the cause of some of the severe side-effects seen during long-term prophylactic use of pyrimethamine/sulfadoxine (27-29). The purpose of this study was to evaluate the prophylactic efficacy against malaria of the combination of daily proguanil plus sulfisoxazole, compared to either drug alone, and to a control group receiving vitamins.

1. MATERIALS AND METHODS

2.1 Study area and population

The study was performed over a period of 17 weeks from October 1986 to February 1987 in the Karen refugee camp of Mae Thawaw located on the Thai-Burmese border. The study population consisted of schoolchildren aged 5 to 16 years. Nearly all study subjects had lived in this forested area with high malaria transmission for at least three years. Chemoprophylactic studies had already been carried out on this study population; the most recent one was completed two months before the start of the present study.

Additional information on the study area, the study population, and the drug sensitivity pattern of *P. falciparum* in this area may be found in previous publications (12,21).

Physical examination of the study population showed no signs of malnutrition.

2.2 Selection of study subjects

Prior to entering the study, subjects were interviewed and examined for signs of chronic illness and for splenomegaly. Blood samples were obtained for laboratory examination and the following values were determined: white blood cells (WBC) with differential count, haematocrit, SGOT, SGPT, alkaline phosphatase, total and direct bilirubin and blood urea nitrogen (BUN). Information sheets and consent forms were explained to the parents of each subject in their native language before they granted permission for their children to enter the study. Children who fulfilled the following criteria were admitted to the study: age 5 to 16 years, haematocrit greater than 25%, WBC count greater than 3000 per mm$^3$, signed parental informed consent for study participation, and no evidence of chronic, debilitating disease other than malaria.

2.3 Study groups

Subjects were stratified according to age, weight, and presence of splenomegaly. Within each stratum, subjects were randomly assigned to one of four study groups.

Group 1, with 92 subjects received proguanil hydrochloride (Imperial Chemical Industries) at a dose of 100 mg daily for those weighing less than 20 kg, or 200 mg daily for those weighing more than 20 kg. Group 2, with 99 subjects, received sulfisoxazole (Gantrisin) in a daily, single dose of 75 mg per kg body weight. Group 3, with 99 subjects, received the combination regimen of proguanil plus sulfisoxazole (dosage as above). Group 4, with 90 subjects, was administered vitamins daily.
A daily dose of 200 mg proguanil, either alone or in combination with chloroquine, has been recommended for adults (19). The corresponding dose for children should be 100 mg for those weighing less than 20 kg, 150 mg for those weighing between 20 and 40 kg, and 200 mg for those weighing over 40 kg (18). However, because of the available pill formulation, subjects weighing between 20 and 40 kg received doses slightly higher than corresponding adult doses of 200 mg.

2.4 Monitoring and follow-up of prophylaxis

Each day subjects were asked a standard set of questions concerning symptoms or side-effects prior to the administration of medication. Each child was identified by his name and photograph, before being administered the appropriate medication in a non-blinded manner by one of the investigators. Subjects were observed to swallow the pills and then consume a small amount of food.

Malaria smears (Giemsa stained thick and thin) were done at weekly intervals and for any complaints of fever, headache, or backache. A minimum of 200 thick fields were examined before reporting a smear negative. Smears showing only gametocytes were tallied as negative. Technicians reading the smears had no knowledge of subjects' study medications. Subjects found to have positive smears for either falciparum or vivax malaria were referred to an on-site clinic staffed by "Médecins sans Frontières" (MSF) for treatment. For falciparum malaria subjects received a single dose of MSP (mefloquine + sulfadoxine + pyrimethamine) plus a single dose of primaquine. For vivax malaria they received four doses of chloroquine plus daily primaquine for 14 days. In this region the efficacy of each treatment regimen is greater than 97% (unpublished data). Therapy was started within 24 hours of slide reading. Subjects received no other antimalarials other than the experimental drugs during the study. The investigators observed all administration of therapeutic medications, except for the second dose of chloroquine, given for vivax malaria. Prophylactic medications were withheld during treatment and restarted 15 days after initiation of vivax therapy or 21 days after falciparum treatment. For those missing appointments, medication and smears were resumed upon return.

In order to minimize the number of subjects presenting with patent or sub-patent parasitaemias at the start of the study, all subjects were screened with weekly smears starting 8 weeks prior to the start of the study. Cases detected during this period were treated with the above regimens (see section 2.3).

Reported symptoms were considered possible side-effects if they occurred while the subject was on prophylactic drugs and were not attributable to malaria infections (i.e., did not occur within five days of diagnosis or while on treatment). Fever was included as one of these symptoms to evaluate the role of sulfadoxazole in preventing bacterial infections. Upon completion of this study subjects were examined for splenomegaly, and laboratory measurements were repeated. Laboratory abnormalities possibly attributable to the test drugs were defined as abnormal values occurring after drug administration with normal pre-drug administration values.

2.5 Data analysis

Data on malaria incidence and drug side-effects were analysed over the entire study period. Survival analysis using man-week units was used to compare the malaria (falciparum and vivax) attack rates among the groups. Only periods (man-weeks) which occurred after at least one negative smear followed by uninterrupted medication administration were counted. When a break in medication administration occurred due, for example, to absence or malaria therapy, that subject was "re-entered" into the study upon demonstration of a negative smear.

The frequency of reported symptoms, considered to be possible drug side-effects, was calculated by tallying episodes (man-days) of reported symptom as well as the number of individuals experiencing each symptom. The denominators, total number of man-days of medication administration, used to calculate frequency of side-effects (Table 3) are
larger than the denominators, total number of man-weeks of uninterrupted medication administration, used to calculate malaria attack rates (Tables 2 and 3). For example, if a subject missed a single day of medicine, that week is not counted in the tally of prophylactic efficacy, but six days of drug administration are tallied for evaluation of side-effects. Specific statistical tests used are described in the results section.

3. RESULTS

The numbers of children assigned to the groups receiving proguanil, sulfisoxazole, proguanil plus sulfisoxazole, and vitamins were 92, 99, 99 and 90, respectively. Measurements prior to the start of the study showed the groups to be comparable with respect to age, weight, frequency of splenomegaly, haematocrit and WBC count (p > .05 for all values, chi-square test for frequency of splenomegaly and analysis of variance for others). See Table 1.

Nine (9.8%), seven (7.1%), eleven (11.1%), and ten (10.8%) of the subjects from the proguanil, sulfisoxazole, proguanil plus sulfisoxazole and vitamin groups, respectively, were absent from the camp during more than 60% of the study (either dropped out or enrolled late), with the remaining subjects missing 2.1%, 1.7%, 2.5%, and 2.9% of their scheduled appointments, respectively.

Falciparum and vivax prophylactic failures and man-weeks of participation (counting only periods of uninterrupted administration of prophylactic medication) for each study week are shown in Table 2. The number of man-weeks of participation varies on account of lapses in medication administration, of subjects being on malaria therapy, and of subjects resuming prophylaxis after absences.

The risk of contracting falciparum malaria was not constant throughout the study period, but the proportion of total weeks participation during the higher transmission period, weeks 1-12 (as seen in the control group), was comparable among groups (proguanil = 71%, sulfisoxazole = 72%, proguanil plus sulfisoxazole = 71%, vitamins = 72%). The risk of contracting vivax malaria was approximately constant throughout the study except during the last two weeks.

Falciparum and vivax prophylactic failures and man-weeks of participation are listed by number of weeks of complete medication administration in Table 3. For falciparum malaria breakthroughs, occurring after at least one negative smear followed by uninterrupted medication administration, there were 10, 15, 1, and 18 in the proguanil, sulfisoxazole, proguanil plus sulfisoxazole, and vitamin groups, respectively. There were significantly fewer failures on proguanil plus sulfisoxazole compared to either proguanil (p < .01), sulfisoxazole (p < .001), or vitamins (p < .001), using survival analysis (Breslow statistic). After at least 8 days of uninterrupted medication administration (negative smears on days 0 and 7), there were 8 failures against P. falciparum with proguanil, 11 with sulfisoxazole, 1 with proguanil plus sulfisoxazole and 13 with vitamins. Similarly, after 15 days (negative smears on days 0, 7 and 14) there were 8, 10, 1, and 10 failures, respectively.

For vivax malaria, there were 16, 9, 0, and 35 breakthroughs on proguanil, sulfisoxazole, proguanil plus sulfisoxazole, and vitamins respectively. Comparison of the vitamin group to each of the others showed levels of significance at or below .005 (survival analysis, Breslow statistics).

P. falciparum prophylactic failures presented with significant parasitaemias and clinical symptoms, as seen in Table 4. It is unlikely that parasitaemias would have spontaneously cleared without treatment, nor would proguanil or sulfisoxazole, used alone, be able to limit parasitaemias once breakthroughs did occur. No subject considered a prophylactic failure reported vomiting of medication prior to positive smears.
Side-effects

Reported symptoms considered to be possible drug side-effects are presented in Table 5 as episodes and number of individuals reporting the symptom. On the whole, symptoms were few, mild, and transient. There was significantly more dizziness, nausea, and vomiting in the proguanil plus sulfisoxazole group compared to controls (p < .001, chi-square). Dizziness was also reported more often in the proguanil group. The group on sulfisoxazole alone, had fewer episodes of fever, headache, and abdominal pain (p < .05, chi-square) than did the control group, but this observation was not true in the group receiving sulfisoxazole plus proguanil.

One subject each from the sulfisoxazole group and the proguanil plus sulfisoxazole group developed urticarial rash which resolved after discontinuation of the initial regimen and inclusion into the vitamin group. Both were ambulatory, and had no trouble eating or drinking. For one subject on proguanil, medication was discontinued because of frequent complaints of headache and dizziness, beginning three months after the start of medication.

Paired blood samples before and after medication administration were obtained on 81, 89, 88, and 77 subjects on proguanil, sulfisoxazole, proguanil plus sulfisoxazole, and vitamins, respectively, and tested for total and direct bilirubin, SGOT, alkaline phosphatase, BUN, haematocrit and WBC. In all four groups, the post-trial haematocrits, WBC counts, and SGPT values were greater by paired t-test (p < .025). Table 6 shows values which were initially normal but became abnormal during the study. For elevated WBC counts, the number of individuals in each group is presented instead of the actual counts. At the time of the second blood sample the camp was experiencing an epidemic of upper respiratory tract infections, the probable cause of elevated WBC counts in all groups.

4. DISCUSSION

In an area of multi-drug resistant P. falciparum a prospective field trial was conducted to test three drug regimens for prophylactic efficacy against both falciparum and vivax malaria. For both types of malaria the combination of proguanil plus sulfisoxazole proved statistically superior to either drug used alone, as well as to the control group. By closely monitoring the study population confined to an endemic area, it was possible to enforce compliance with medication administration and reporting of side-effects, to conduct adequate follow-up for case detection, to restrict self-administration of non-study antimalarials, and to ensure equal malaria risk among study groups.

In addition, this study provides data which support previous suggestions that proguanil offers poor protection against South-East Asian strains of P. falciparum (19,21,30). Breakthroughs occurring after at least one negative smear followed by uninterrupted medication administration represent suppressive prophylactic failures. If medications were administered throughout the prepatent period as well, then breakthroughs represent both suppressive and causal prophylactic failures. Of the 10 breakthroughs on proguanil, 8 occurred after more than two weeks of medication administration. These failures represent either: (a) suppressive failures following long-standing subpatent infections, (b) suppressive failures following prolonged prepatent periods, or (c) causal (and suppressive) failures. Long-standing subpatent infections are unlikely because of the low malaria immunity of the study population, evidenced by low prevalence of splenomegaly and presence of symptoms and significant parasitaemias at the time of slide confirmation. Furthermore, during weekly screening for eight weeks prior to the start of the study, subjects either remained negative or were administered an effective therapy for falciparum malaria. Though certain antimalarials, notably the sulfonamides, can significantly prolong prepatent periods, a small study by Clyde et al. showed that proguanil lengthened the prepatent period an average of only one day (range 1-3 days) (31). In the light of the above observations, these eight breakthroughs probably represent causal prophylactic failures, implying a causal prophylactic efficacy of approximately 50%.
It is hoped, though not certain, that the findings of this study can be extrapolated to non-immune populations. The study population may have a low degree of immunological protection and therefore a non-immune group administered proguanil plus sulfisoxazole would perhaps receive poorer protection under similar malaria exposure. The same argument applies to proguanil used alone, with the possibility that efficacy in non-immunes would be lower than what has been shown in this study.

For logistic reasons and ethical constraints, *P. falciparum* isolates from prophylactic breakthroughs were not routinely tested for *in vitro* drug sensitivities, nor were blood samples obtained for serum drug levels. Since it is unknown whether the proguanil plus sulfisoxazole regimen is acting as a causal and/or suppressive prophylactic, it was considered uncertain whether *in vitro* drug sensitivity testing on the blood stages would truly reflect prophylactic efficacy. Other investigators feel that there is a correlation in the development of parasite resistance to proguanil between the exoerythrocytic and the erythrocytic stages (32).

It is felt that the Thai strain of *P. falciparum* is so highly drug resistant that prophylactic regimens, such as proguanil plus sulfisoxazole, which have been shown to be effective in this region are probably effective in all other areas of the world. Conversely, regimens which show poor efficacy in this region such as proguanil, may still provide significant protection in other regions where strains are less drug resistant. However, before recommendations for proguanil prophylaxis (either alone or in combination with other drugs) are made in those regions, efficacy should be shown in well controlled trials.

The 1-2% incidence of dermal reactions in subjects on sulfisoxazole seen in this study is not surprising (33). However, there was no occurrence of more severe toxic reactions such as Stevens-Johnson syndrome or agranulocytosis/leukopenia, a significant drawback for prophylactic use of longer acting sulfonamides against *P. falciparum* (8,30,34,35). Much larger groups than the small numbers of the present study need to be monitored for side-effects before general recommendations on the use of proguanil plus sulfisoxazole can be considered. Therefore, although it is not possible to advocate general use of this drug combination at this time, the results of this investigation can serve as a basis for future studies evaluating malaria prophylaxis and side-effects of this combination. Such studies should include: (1) close monitoring of subjects for side-effects; (2) evaluation of lower doses and alternate, analogous drugs; (3) development of *in vitro* tests to correlate with *in vivo* sensitivity patterns; (4) determination of the mechanism of prophylactic action, causal or suppressive; (5) evaluation of efficacy in non-immune populations and in other geographical areas with different drug sensitivity patterns of *P. falciparum*.

In accordance with World Health Organization guidelines (36), the authors do not advocate the use of any drug for general, mass chemoprophylaxis. Effective, safe agents should be reserved for high risk groups, notably pregnant women and non-immune travellers to endemic areas. Chemoprophylaxis might also be considered for short-term use by specific populations in controlled settings, such as labour forces or military units.

5. SUMMARY

In a field trial conducted on the Thai-Burmese border, an area of multi-drug resistant *Plasmodium falciparum*, daily proguanil plus sulfisoxazole was tested for prophylactic efficacy against falciparum and vivax malaria. Children, aged 5-16 years, whose parents had given informed consent for their participation in the study, were stratified according to age, weight, and presence of splenomegaly, and were then randomly assigned to one of four study groups:

(1) 92 subjects received proguanil (100 mg daily for those weighing less than 20 kg and 200 mg for those weighing more than 20 kg);

(2) 99 subjects received sulfisoxazole (75 mg per kg body weight daily in a single dose);
(3) 99 subjects received the combination regimen of proguanil plus sulfisoxazole (dosage as above);

(4) 90 subjects, who served as control group, received vitamins daily.

All doses of medication were administered in a non-blinded manner by the investigators. No child received antimalarials other than the study drugs or the drugs required for malaria treatment (mefloquine/sulfadoxine/pyrimethamine for falciparum malaria or chloroquine plus primaquine for vivax malaria). The investigators supervised the administration of all medications. Children were interviewed daily for symptoms, including possible side-effects of the study drugs. Blood samples for laboratory tests were obtained at the beginning and at the end of the study. Malaria smears were made for all subjects weekly and at the time of any complaints suggestive of malaria. Investigators performed the slide readings without knowing to which group the subjects belonged. Before reporting a slide as negative, 200 thick fields were examined.

The study was conducted over a period of 17 weeks from October 1986 to February 1987. The 92, 99, 99 and 90 children assigned to the proguanil, sulfisoxazole, proguanil plus sulfisoxazole, and vitamin groups, respectively, accounted for 1300, 1425, 1464, and 1303 man-weeks of uninterrupted medication administration, respectively. There were 10, 15, 1, and 18 P. falciparum breakthroughs and 15, 9, 0, and 35 P. vivax breakthroughs in the proguanil, sulfisoxazole, proguanil plus sulfisoxazole, and vitamin groups, respectively. The drug combination regimen proved statistically superior to either drug used alone as well as to the vitamins of the control group, for protection against falciparum and vivax malaria. Notably, of the 10 falciparum breakthroughs in the proguanil group, 8 occurred after at least two weeks of medication administration (negative smears on days 0, 7, 14), and this is suggestive of causal failures. On the whole, symptoms were mild and transient, with the group on the combined regimen reporting more dizziness, nausea, and vomiting compared to controls. Urticarial rash developed in two subjects on sulfisoxazole. Laboratory abnormalities (complete blood count, liver function tests, blood urea nitrogen) in the treatment groups were unremarkable compared to those of the control group.

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RESUME

PROPHYLAXIE ANTIPALUSTRE CHEZ L'ENFANT AU MOYEN DE PROGUANIL ET SULFISOXAZOLE EN REGION D'ENDEMIE

Lors d'un essai de terrain effectué à la frontière birmano-thaïlandaise, une région où Plasmodium falciparum est multi-résistant, on a expérimenté l'administration, à titre prophylactique, de doses quotidiennes de proguanil plus sulfisoxazole contre le paludisme à falciparum et vivax. Après accord des parents en connaissance de cause, les enfants âgés de 5 à 16 ans ont été stratifiés selon l'âge, le poids et la présence d'une splénomégalie puis répartis aléatoirement dans l'un des quatre groupes suivants :

1) 92 sujets sous proguanil (100 mg par jour pour un poids corporel de moins de 20 kg, et 200 mg par jour au-delà);
2) 99 sous sulfisoxazole (75 mg par kg de poids corporel et par jour en prise unique);
3) 99 sous proguanil plus sulfisoxazole (même dosage que précédemment);
4) 90 sujets, sous traitement vitaminique quotidien (groupe témoin).

Toutes les posologies étaient connues des chercheurs. Aucun enfant n'a reçu d'autres antipaludiques que ceux de l'étude ou que ceux nécessaires au traitement de la maladie (méfloquine/sulfadoxine/pyriméthamine pour le paludisme à falciparum ou chloroquine plus primaquine pour le paludisme à vivax). Les chercheurs ont supervisé l'administration de tous les médicaments. On a interrogé les enfants chaque jour à la recherche de symptômes, notamment d'effets secondaires possibles de ces médicaments. On a prélevé des échantillons de sang pour des analyses de laboratoire au début et à la fin de l'étude. Des frottis sanguins ont été effectués pour tous les sujets une fois par semaine et chaque fois qu'ils se plaignaient de symptômes de type palustre. Les chercheurs ont examiné les lames sans savoir à quel groupe les sujets appartenaient. Avant d'enregistrer une lame comme négative, on a examiné 200 champs microscopiques de l'étalement épais.

L'étude a duré 17 semaines, d'octobre 1986 à février 1987. Les 92, 99, 99, et 90 enfants à qui l'on a donné respectivement du proguanil, du sulfisoxazole, du proguanil plus sulfisoxazole et des vitamines représentaient respectivement 1300, 1425, 1464, et 1303 semaines-homme de traitement ininterrompu. Il y a eu respectivement 10, 15, 1, et 18 poussées de paludisme à falciparum et 15, 9, 0, et 35 poussées de paludisme à vivax dans les groupes sous proguanil, sulfisoxazole, proguanil plus sulfisoxazole et vitamines. L'association s'est révélée statistiquement meilleure à chaque substance utilisée seule ainsi qu'au traitement vitaminique, en ce qui concerne la protection contre le paludisme à falciparum et à vivax. Il est à noter que sur les dix poussées à falciparum dans le groupe sous proguanil, huit se sont produites au bout d'au moins deux semaines de prise de médicaments (frottis négatifs aux jours 0, 7, et 14), ce qui évoque l'échec causal. Dans l'ensemble les symptômes ont été bénins et transitoires, le groupe recevant l'association n'ayant signalé davantage de vertiges, de nausées et de vomissements par rapport au témoin. Une éruption urticarienne est apparue chez deux sujets du groupe sous sulfisoxazole. Il n'y avait pas eu de différences notables dans les anomalies relevées au laboratoire (NFS, épreuve de la fonction hépatique, azote uréique du sang) entre les groupes traités et le groupe témoin.

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### TABLE 1. BASELINE CHARACTERISTICS OF CHILDREN RECEIVING EITHER PROGUANIL, SULFISOXAZOLE, PROGUANIL + SULFISOXAZOLE, OR VITAMINS, MAE THAWAW, OCTOBER 1986 - FEBRUARY 1987

<table>
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<th></th>
<th>Proguanil</th>
<th>Sulfisoxazole</th>
<th>Proguanil + sulfisoxazole</th>
<th>Vitamins</th>
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<td></td>
<td>n = 92</td>
<td>n = 99</td>
<td>n = 99</td>
<td>n = 90</td>
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<td>Mean age (years)</td>
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<td>9.7</td>
<td>9.5</td>
<td>9.5</td>
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<tr>
<td>Mean weight (kg)</td>
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<td>23.4</td>
<td>23.2</td>
<td>22.6</td>
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<td>Splenomegaly (%)</td>
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<td>13.3</td>
<td>12.1</td>
<td>12.0</td>
</tr>
<tr>
<td>Mean haematocrit (%)</td>
<td>38.7</td>
<td>38.5</td>
<td>39.0</td>
<td>38.2</td>
</tr>
<tr>
<td>Mean WBC count (per mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>8546</td>
<td>9257</td>
<td>8695</td>
<td>9062</td>
</tr>
</tbody>
</table>

### TABLE 2. CASES OF MALARIA AND PARTICIPATION BY STUDY WEEK AMONG CHILDREN ADMINISTERED DAILY PROGUANIL, SULFISOXAZOLE, PROGUANIL + SULFISOXAZOLE, OR VITAMINS, MAE THAWAW, OCTOBER 1986 - FEBRUARY 1987

<table>
<thead>
<tr>
<th>Week No.</th>
<th>Proguanil</th>
<th>Sulfisoxazole</th>
<th>Proguanil + sulfisoxazole</th>
<th>Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 92</td>
<td>n = 99</td>
<td>n = 99</td>
<td>n = 90</td>
</tr>
<tr>
<td>1,2 (10 October)</td>
<td>1/148 (0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0/173 (0)</td>
<td>0/176 (0)</td>
<td>3/163 (4)</td>
</tr>
<tr>
<td>3,4</td>
<td>1/166 (1)</td>
<td>1/178 (0)</td>
<td>0/186 (0)</td>
<td>2/157 (3)</td>
</tr>
<tr>
<td>5,6</td>
<td>2/152 (6)</td>
<td>3/173 (2)</td>
<td>1/176 (0)</td>
<td>4/158 (5)</td>
</tr>
<tr>
<td>7,8</td>
<td>1/153 (4)</td>
<td>2/173 (0)</td>
<td>0/175 (0)</td>
<td>0/161 (5)</td>
</tr>
<tr>
<td>9,10</td>
<td>2/153 (2)</td>
<td>2/163 (0)</td>
<td>0/167 (0)</td>
<td>3/153 (6)</td>
</tr>
<tr>
<td>11,12</td>
<td>2/154 (1)</td>
<td>4/168 (4)</td>
<td>0/161 (0)</td>
<td>4/151 (4)</td>
</tr>
<tr>
<td>13,14</td>
<td>1/148 (0)</td>
<td>0/152 (3)</td>
<td>0/162 (0)</td>
<td>1/142 (4)</td>
</tr>
<tr>
<td>15,16</td>
<td>0/151 (1)</td>
<td>2/163 (0)</td>
<td>0/175 (0)</td>
<td>1/144 (3)</td>
</tr>
<tr>
<td>17 (15 February)</td>
<td>0/75 (1)</td>
<td>1/82 (0)</td>
<td>0/86 (0)</td>
<td>0/74 (1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10/1300 (16)</strong></td>
<td><strong>15/1425 (9)</strong></td>
<td><strong>1/1464 (0)</strong></td>
<td><strong>18/1303 (35)</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> Cases of falciparum malaria/man-week (cases of vivax malaria in parentheses).
### TABLE 3. CASES OF MALARIA AND PARTICIPATION BY WEEKS OF COMPLETE MEDICATION ADMINISTRATION AMONG CHILDREN ADMINISTERED DAILY PROGUANIL, SULFISOXAZOLE, PROGUANIL + SULFISOXAZOLE, OR VITAMINS, MAE THAWAIG, OCTOBER 1986 - FEBRUARY 1987

<table>
<thead>
<tr>
<th>Weeks on uninterrupted medication</th>
<th>Proguanil n = 92</th>
<th>Sulfisoxazole n = 99</th>
<th>Proguanil + sulfisoxazole n = 99</th>
<th>Vitamins n = 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2</td>
<td>2/320 (3)</td>
<td>5/351 (1)</td>
<td>0/324 (0)</td>
<td>8/316 (12)</td>
</tr>
<tr>
<td>3, 4</td>
<td>4/253 (6)</td>
<td>2/264 (2)</td>
<td>1/266 (0)</td>
<td>3/250 (8)</td>
</tr>
<tr>
<td>5, 6</td>
<td>1/192 (4)</td>
<td>3/202 (2)</td>
<td>0/213 (0)</td>
<td>4/192 (4)</td>
</tr>
<tr>
<td>7, 8</td>
<td>1/146 (1)</td>
<td>2/166 (0)</td>
<td>0/177 (0)</td>
<td>1/154 (6)</td>
</tr>
<tr>
<td>9, 10</td>
<td>1/122 (2)</td>
<td>1/133 (3)</td>
<td>0/145 (0)</td>
<td>1/121 (4)</td>
</tr>
<tr>
<td>11, 12</td>
<td>1/95 (0)</td>
<td>2/110 (1)</td>
<td>0/118 (0)</td>
<td>1/96 (0)</td>
</tr>
<tr>
<td>13, 14</td>
<td>0/74 (0)</td>
<td>0/88 (0)</td>
<td>0/98 (0)</td>
<td>0/78 (0)</td>
</tr>
<tr>
<td>15, 16</td>
<td>0/68 (0)</td>
<td>0/75 (0)</td>
<td>0/86 (0)</td>
<td>0/67 (1)</td>
</tr>
<tr>
<td>17</td>
<td>0/30 (0)</td>
<td>0/36 (0)</td>
<td>0/37 (0)</td>
<td>0/29 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>10/1300 (16)</td>
<td>15/1425 (9)</td>
<td>1/1464 (0)</td>
<td>18/1303 (35)</td>
</tr>
</tbody>
</table>

* Cases of falciparum malaria/man-week (cases of vivax malaria in parentheses).

### TABLE 4. SUPPRESSIVE PROPHYLACTIC FAILURES: PRESENCE OF PARASITAEMIA AND OCCURRENCE OF CLINICAL SYMPTOMS

<table>
<thead>
<tr>
<th>Parasite count (per 100 WBC)</th>
<th>Proguanil</th>
<th>Sulfisoxazole</th>
<th>Proguanil + sulfisoxazole</th>
<th>Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>1*</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>1 - 10</td>
<td>4 (1)</td>
<td>6</td>
<td>5 (1)</td>
<td>3</td>
</tr>
<tr>
<td>11 - 100</td>
<td>2 (1)</td>
<td>3</td>
<td>5 (2)</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>4 (4)</td>
<td>1</td>
</tr>
</tbody>
</table>

* Entries are numbers of *P. falciparum* (P.f.) or *P. vivax* (P.v.) cases, with in parentheses the numbers of cases with symptoms at time of diagnosis.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Proguanil</th>
<th>Sulfadoxine</th>
<th>Proguanil + sulfadoxine</th>
<th>Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episodes</td>
<td>Individuals</td>
<td>Episodes</td>
<td>Individuals</td>
</tr>
<tr>
<td></td>
<td>(man-days)</td>
<td>(man-days)</td>
<td>(man-days)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>127</td>
<td>44</td>
<td>107(^b)</td>
<td>40</td>
</tr>
<tr>
<td>Headache</td>
<td>84</td>
<td>24</td>
<td>52(^b)</td>
<td>26</td>
</tr>
<tr>
<td>Dizziness</td>
<td>68(^a)</td>
<td>25</td>
<td>42</td>
<td>19</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>7</td>
<td>8(^b)</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10</td>
<td>7</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Total number of man-days on study drug</td>
<td>10 964</td>
<td>11 764</td>
<td>11 720</td>
<td>11 084</td>
</tr>
</tbody>
</table>

\(^a\) Greater than control group (p < .05), chi-square.
\(^b\) Less than control group (p < .05).
<table>
<thead>
<tr>
<th></th>
<th>Proguanil n = 81</th>
<th>Sulfisoxazole n = 89</th>
<th>Proguanil + sulfisoxazole n = 88</th>
<th>Vitamins n = 77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit (&lt; 30%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>WBC countb (&gt; 11 500 per mm³)</td>
<td>27</td>
<td>16</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Bilirubin (&gt; 1.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SGPT (&gt; 45)</td>
<td>46, 160</td>
<td>125, 92, 48</td>
<td>48</td>
<td>48, 48</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>46</td>
<td></td>
<td>52</td>
</tr>
<tr>
<td>SGOT (&gt; 50)</td>
<td>60, 52, 112, 60, 55</td>
<td>69, 52, 58</td>
<td>58, 80, 63, 65, 55, 60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>66, 52, 72, 72</td>
<td>66</td>
<td>58, 58, 143, 52, 60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52, 51</td>
<td></td>
<td></td>
<td>52, 60</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(&gt; 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (&gt; 25)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a Abnormal values are shown in table.
b Gives numbers of individuals with elevated WBC counts.