Therapeutic efficacy of chloroquine or amodiaquine in combination with sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in Papua New Guinea

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SUMMARY

Resistance of Plasmodium falciparum to chloroquine is widespread in Papua New Guinea. At a meeting in Port Moresby in October 1997, it was decided to explore a possible change of the current first-line treatment of uncomplicated malaria with chloroquine alone (amodiaquine for children under five years) to chloroquine or amodiaquine in combination with sulfadoxine-pyrimethamine (S-P). To assess the therapeutic efficacy of the new drug combination in Papua New Guinea, a study was carried out in 1998-1999 at five hospital outpatient departments. From the 513 patients enrolled for the study, 95 defaulted from follow-up. Of the remaining 418, 399 (95.5%) had an adequate clinical response (ACR). Out of the 19 patients who did not have an ACR, 3 (0.7% of the total) developed severe signs in the first 24 hours and were treated in hospital; they were regarded as early treatment failures. The remaining 16 did not complete the study on the basis of various exclusion criteria but were not excluded from the analysis. From these results it was concluded that the combination was effective and a decision was taken in May 2000 to introduce the two-drug combination regimen as the standard first-line treatment of uncomplicated malaria, including falciparum malaria, in Papua New Guinea.

Introduction

Resistance of Plasmodium falciparum to 4-aminopyrimidines (chloroquine and amodiaquine) is a common problem in nearly all parts of the world where transmission of malaria due to this parasite occurs (1,2). In the World Health Organization (WHO) Western Pacific Region, chloroquine-resistant Plasmodium falciparum was detected for the first time in Irian Jaya (Indonesia) in 1974 (3), and also in Papua New Guinea (PNG) during 1976 (4,5). Since then a number of studies on the susceptibility of P. falciparum to chloroquine and other currently used antimalarials have been carried out in Papua New Guinea, where the standard first-line treatment for falciparum malaria and clinically diagnosed malaria is chloroquine for those aged 5 years and above and amodiaquine for children under 5 years. These studies had shown 51% R1,
22% R2 and 14% R3 level resistance to chloroquine in East New Britain Province in 1980 (6). In Madang Province during the period 1979-1983 there was 42-46% R1, 3-4% R2 and 2-4% R3 resistance to chloroquine (7,8). In Western Province chloroquine resistance was 33% R1, 10% R2 and 3% R3 during the period 1986-1990 (9,10). The level of resistance to amodiaquine was 22-24% and to quinine was 7% in the Madang and East Sepik provinces (11-13). Experience during a number of malaria epidemics which occurred in the highland provinces during the last decade indicated that chloroquine was no longer effective against *Plasmodium falciparum* (14). At a workshop on antimalarial drug policy convened by the Department of Health in 1997, a decision was made to assess the therapeutic efficacy of chloroquine/amodiaquine in combination with sulfadoxine-pyrimethamine (S-P) (Fansidar). This combination had been in use in Vanuatu for a number of years with good results and if the efficacy were to prove satisfactory, it would be adopted in Papua New Guinea as the standard first-line treatment for uncomplicated falciparum malaria and by extension all uncomplicated malaria.

**Materials and Methods**

The test system which was followed aimed to assess the proportion of patients with an adequate clinical response (ACR) in the sample of patients included in the study. The statistical procedure adopted for the interpretation of the results allowed us to test whether the proportion of ACR was above 95% at a p value of <0.05 for the null hypothesis; in this case we would conclude that the drug combination was effective and the results statistically significant.

Five hospitals from various areas representing different malarious strata of the country were selected to conduct the study (Figure 1). Children and adults who attended the outpatient sections of these hospitals with uncomplicated falciparum malaria were eligible to be included. As the response to the drugs could vary according to the level of immunity of the patient (15), it was decided to have three age groups: 6-59 months, 5-14 years and 15 years and over. 50 patients from each group would be studied at each centre and the total sample from the five centres was expected to be 750. The WHO document *Assessment of Therapeutic Efficacy of Antimalarial Drugs for Uncomplicated Falciparum Malaria in Areas with Intense Transmission* (16) was the basis for the protocol of the study. The antimalarial drugs used were from single batches which had been quality controlled at an independent laboratory.

**Inclusion criteria**

To be included in the study, patients had to have a history of fever during the previous 24 hours and a mono-infection of *P. falciparum* with parasite counts between 1000 and 200,000/µl of blood without signs of severe disease requiring hospitalization. There had to be no other condition which could cause fever, no history of hypersensitivity to any drug and no skin condition such as eczema. Patients with severe malnutrition or any chronic disease were not included in the study.

**Exclusion criteria (after enrolment)**

Those who developed severe signs of any concomitant disease that needed additional treatment or interfered with the classification of the treatment outcome were excluded from the study and treated according to their condition. Detection of a mixed infection during the follow-up period or failure to complete the treatment or follow-up due to the withdrawal of consent led to exclusion from the study. Those patients in whom any antimalarial treatment was given by a third party during the follow-up period were also excluded from the study. Previous treatment with antimalarials was not a criterion for exclusion; however, the information was recorded.
Defaulters

Those patients lost to follow-up despite fulfilling all inclusion criteria, without developing any exclusion criteria during the follow-up period, were considered as defaulters.

Early treatment failure

The therapeutic response was classified as early treatment failure (ETF) if the patient developed any of the following conditions during the first three days of follow-up:

- signs of severe malaria on Day 1, Day 2 or Day 3 in the presence of parasitaemia;
- axillary temperature $\geq 37.5^\circ C$ on Day 2 with parasitaemia $> Day 0$ count;
- axillary temperature $\geq 37.5^\circ C$ on Day 3 with parasitaemia; or
- parasitaemia on Day 3 $\geq 25\%$ of count on Day 0.

Late treatment failure

The therapeutic response was classified as late treatment failure (LTF) if the patient developed any of the following conditions during the follow-up period from Day 4 to Day 14:

- signs of severe malaria in the presence of parasitaemia on any day from Day 4 to Day 14, without previously meeting any of the criteria for early treatment failure; or
- axillary temperature $\geq 37.5^\circ C$ in the presence of parasitaemia on any day from Day 4 to Day 14 without previously meeting any of the criteria for early treatment failure.

Figure 1. Map of Papua New Guinea showing the provincial location of the five study centres.
Adequate clinical response

The therapeutic response was classified as an adequate clinical response (ACR) when the patient showed any of the following conditions during the follow-up period of 14 days:

- absence of parasitaemia on Day 14 irrespective of axillary temperature, without previously meeting any of the criteria of ETF or LTF; or
- axillary temperature <37.5°C irrespective of the presence of parasitaemia, without previously meeting any of the criteria of ETF or LTF.

Test procedure

Five hospitals representing the three main epidemiological malaria strata of the country participated in the study. The hyperendemic coastal lowlands were represented by Angau Memorial Hospital – Lae, Boram General Hospital – Wewak, and Modilon General Hospital – Madang. The mesoendemic fringe highlands were represented by the Ok Tedi Mining Limited Hospital (OTML) – Tabubil, and the highlands with epidemic and imported malaria by Tinsley District Hospital – near Mt Hagen.

Technicians from the five centres were trained for five days on the study at the training laboratory at the Malaria Surveillance and Control Unit (MSCU) in Goroka and provided with the supplies needed for the study. To reduce the workload, the number of patients to be enrolled in one day was limited to a maximum of five at each centre. After the patient had been screened by a nurse, capillary blood was taken for thick and thin smears by a technician. Those whose blood films were positive (within the limits stipulated in the study protocol) were given a full clinical examination by a medical doctor and were enrolled in the study. Informed consent of the patient (or parent/guardian of children) was obtained on a special form written in Melanesian Pidgin after the contents had been explained. The patients were weighed, axillary temperature was recorded to one decimal point and in children aged between 6 months and 12 years haemoglobin levels were measured on Day 0 and on Day 14. Table 1 summarizes information on the patients who enrolled and defaulted, were excluded or completed the study.

Daily administration of drugs (Table 2) and other follow-up activities were done by a nurse. Each patient received a card to facilitate priority access to health care during the study period. To ensure follow-up, the patients were given an incentive of K2.00 (US$0.70) for each visit to cover bus fares and other minor expenses.

All blood slides with the results were sent once a week to the MSCU laboratory and checked blindly by another technician. The cross-checked results were sent to the study centres within a week with advice to replace the result in case of discrepancy. Data from patients were recorded on paper forms at the study centres by the health workers and later entered on Epi Info data files for summary and analysis. Analysis was done according to the protocol, excluding the defaulters, but to be conservative, on a partial intention-to-treat basis, all patients who satisfied exclusion criteria, for whatever reason, were included in the analysis. Table 3 gives the parasite density of the patients by malaria stratum and age group at the pretreatment examination on Day 0. There was not much difference in the parasite densities in the three strata, but densities tended to be higher in young children in all areas.

Results

Out of 513 enrolled from the five centres there were 95 defaulters, 3 early treatment failures and 16 exclusions; 399 completed the study. The highest number of defaulters was from Boram Hospital. Most of the defaulters took the full course of treatment, but did not turn up for follow-up. Two children under five years from Boram were excluded.
from follow-up because they developed febrile convulsions a few hours after treatment. One adult patient from the same centre had severe vomiting a few hours after taking chloroquine. These three patients were referred for in-patient treatment and were considered as early treatment failures. At Angau Hospital one patient was excluded because the blood film was found to be negative on cross-checking. At Tabubil Hospital, one patient was excluded because a mixed infection was detected on rechecking.

**TABLE 1**

**Patients who enrolled and defaulted, were excluded or completed the study in the five study centres**

<table>
<thead>
<tr>
<th>Hospital</th>
<th>No enrolled</th>
<th>No defaulted</th>
<th>No excluded*</th>
<th>No completed the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;5 years</td>
<td>5-14 years</td>
<td>&gt;15 years</td>
<td>Total</td>
</tr>
<tr>
<td>Angau</td>
<td>10</td>
<td>17</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>Boram</td>
<td>36</td>
<td>57</td>
<td>70</td>
<td>163</td>
</tr>
<tr>
<td>Modilon</td>
<td>55</td>
<td>55</td>
<td>47</td>
<td>157</td>
</tr>
<tr>
<td>Tabubil</td>
<td>11</td>
<td>47</td>
<td>52</td>
<td>110</td>
</tr>
<tr>
<td>Tinsley</td>
<td>4</td>
<td>11</td>
<td>28</td>
<td>43</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>116</strong></td>
<td><strong>187</strong></td>
<td><strong>210</strong></td>
<td><strong>513</strong></td>
</tr>
</tbody>
</table>

*Includes early treatment failures: none of these patients were excluded from the analysis.

**TABLE 2**

**Drug dosages in tablets by weight group in the study**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Chloroquine 150 mg</th>
<th>Amodiaquine 100 mg</th>
<th>S-P 500+25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 0</td>
</tr>
<tr>
<td>5 - 9 kg</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10 - 14 kg</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15 - 19 kg</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20 - 29 kg</td>
<td>1½</td>
<td>1½</td>
<td>1½</td>
</tr>
<tr>
<td>30 - 39 kg</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>40 - 49 kg</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

S-P: 500 mg sulfadoxine and 25 mg pyrimethamine per tablet
the blood film. The remaining exclusions were due to various reasons unrelated to malaria. No other case of severe malaria, ETF, LTF or fatality was recorded among those enrolled.

The outcome of treatment is presented in Tables 4 to 6. Table 4 gives the parasite clearance and fever/symptom clearance in the patients included in the study. Of the 513 malaria patients with positive blood films included in the study, 161 (31%) were non-febrile at the time of presentation (Day 0), but gave a history of fever during the previous 24 hours. 498 of them presented for examination/medication the following day (Day 1) and 468 of them were free of symptoms and non-febrile, giving a fever/symptom clearance rate of 94%. Fever/symptom clearance was 99% on Day 2 (483 out of 487) and 100% on Day 3 (464 out of 464). Out of those who returned, there was no recurrence of fever, clinical symptoms or parasitaemia during the 14-day follow-up period. One patient under five years from Boram Hospital had a positive blood film on Day 3 examination. The parasite density was less than 25% of the Day 0 results and was negative on Day 7 and Day 14 follow-up films. Hence, the case can be classified as ACR.

Table 5 gives the therapeutic response of the patients by treatment centre. Out of the 19 patients who did not have an ACR, 3 developed severe signs and were considered as early treatment failures, giving a rate of 0.7% for this category of therapeutic response. There were no late treatment failures at any of the centres. The adequate clinical response rate in the sample of patients included in the study was 95.5%.

The children enrolled were marginally anaemic. Fourteen days after treatment, their haemoglobin levels had improved by an average 1.7 g/dl (CI 1.5-1.9) (Table 6). The

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**TABLE 3**

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Parasite density</th>
<th>Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;5 years</td>
</tr>
<tr>
<td>Highlands</td>
<td>Maximum</td>
<td>100000</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>7400</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>2800</td>
</tr>
<tr>
<td>Lowlands</td>
<td>Maximum</td>
<td>95000</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>13725</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>1000</td>
</tr>
<tr>
<td>Fringe Highlands</td>
<td>Maximum</td>
<td>100000</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>27400</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>5400</td>
</tr>
</tbody>
</table>
improvement is statistically significant.

Discussion and Conclusions

The planned sample sizes were not reached. However, when the data are combined to represent the three epidemiological malaria strata (and this is justified by the homogeneity of the results), the sample sizes were adequate, except for the highlands where malaria patients under 5 years are rare.

The main result of the study is that, out of 513 patients who met the inclusion criteria, 399 completed the study and were found to have an adequate clinical response. Despite good efforts to track the patients, there were 19% defaulters. Practically all the defaulters had taken the full course of treatment, but did not come for follow-up examinations. In rural Papua New Guinea, where the study took place, there are practically no alternative sources of malaria treatment and it is therefore unlikely that there were clinical failures among the defaulters. The group of
patients who did not complete the study for various reasons includes the three patients whose symptoms worsened during the first 24 hours; though they were considered as early treatment failures, there was no evidence that their parasites were resistant to the treatment.

To take a conservative approach to the estimation of clinical response rates, we stratified by age group and by epidemiological stratum and included the excluded patients in the denominator in our analysis. Table 7 shows that in each stratum under each age group, the lower limit of the confidence interval of ACR is ≥79.2% except where numbers were small. In these cases there is a wider confidence interval which is caused by the smaller sample size and not by any difference in the results. When the results are considered overall, the clinical response rate is above 95% and the results are statistically significant.

In children whose haemoglobin was checked on Day 0 and on Day 14, there was an average improvement in the haemoglobin levels of about 1.7 g/dl (CI 1.5-1.9) and this
is further evidence of the efficacy of the combination treatment. In endemic areas, the clinical response rate of 95.5% (CI 93.8-97.2) that we have observed in a 14-day follow-up is considered satisfactory.

Good results could not have been obtained with S-P alone. This is because early in vivo studies in Papua New Guinea found that \textit{P. falciparum} already showed some resistance to this drug (17). Also, S-P alone is not a very effective treatment for vivax malaria and most malaria cases in PNG are treated without a parasitological diagnosis. More importantly, combination therapy with different drugs is recommended because it has major advantages in therapy and in slowing the evolution of drug resistance in the parasite.

According to current knowledge, the alternative regimen would be a combination of an artemisinin drug with another schizontocide (18). Such a treatment costs over K6.00 (US$2.00) per adult course, which is considerably more than the cost of K0.60-0.70 (US$0.20-0.30) for chloroquine with S-P. This difference is important in a country where the population relies on the state and the church health services for free curative care and clinical malaria affects about one in four persons per year.

No side-effects were recorded. The study was not planned to determine the prevalence of side-effects with the test treatments, which are expected to be very rare, though sometimes serious. Yet the study adds to the evidence that combinations of amodiaquine or chloroquine with S-P are safe enough to be used for the treatment of uncomplicated malaria (19,20). We conclude that the combination of chloroquine or amodiaquine with sulfadoxine and pyrimethamine (S-P) (Fansidar) as the standard first-line treatment in Papua New Guinea for uncomplicated malaria, including falciparum malaria. The use of this combination as the first-line treatment is expected to reduce the number of treatment failures, the incidence of severe malaria and malaria mortality.

**ACKNOWLEDGMENTS**

This study was funded by WHO through its Regional Office for the Western Pacific. We are very grateful to the clinical and technical staff who assisted in the study at the five centres. The support and the assistance by the staff of MSCU, Goroka, was of great help in organizing and coordinating the study. The encouragement by Dr Puka Temu, Secretary for Health, to carry out the study was of crucial importance. The advice of Dr Michael Alpers, Director, Papua New Guinea Institute of Medical Research, Goroka, was very much appreciated. The assistance provided by Dr Steven Bjorge, WHO scientist, in the data analysis and other matters was of great value. Special mention has to be made of the interest shown and assistance provided by Drs Kevin Palmer and Allan Schapira, from the WHO Regional Office for the Western Pacific.

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