THERAPEUTIC EFFICACY OF SULFADOXINE-PYRIMETHAMINE AND AMODIAQUINE AMONG CHILDREN WITH UNCOMPROMICATED PLASMODIUM FALCIPARUM MALARIA IN ZANZIBAR, TANZANIA

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Abstract. The efficacy of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) was assessed at Kivunge and Micheweni in Zanzibar, Tanzania, in 2001. The main objective was to obtain baseline data after observations of high levels of chloroquine treatment failures. Children (6–59 months) were randomized to receive either drug. At Kivunge, SP and AQ were given to 64 and 63 cases, while for Micheweni, 61 and 70 cases were treated. Main findings were overall high rates (>90%) of adequate clinical response (ACR) with AQ. A lower ACR was seen in the SP group at Kivunge (87.1%) compared with Micheweni (94.8%). Furthermore, in the ACR group, 16.7% AQ parasitological resistance (RI–RIII) was encountered at Kivunge. Most of the cases of SP parasitological resistance (14.5%; RI/RII) were seen at Micheweni. Notwithstanding this, the overall treatment failure was only 9.2% with SP and 5.5% with AQ. The Zanzibar Ministry of Health has since reviewed its antimalarial drug policy.

INTRODUCTION

Chloroquine resistance in indigenous Tanzanians first reported in 1982 is now widespread.1 Despite vast data on the response of Plasmodium falciparum to chloroquine (CQ) and other antimalarials for mainland Tanzania, it is rather scarce for Zanzibar.2 A number of studies have shown better efficacy with AQ compared with CQ or sulfadoxine-pyrimethamine.3,4 Documenting treatment failures in health facility setting using the standard WHO protocol5 would provide the needed data to review and update antimalarial drug policy in Zanzibar.

The WHO protocol used here involves a 14-day follow-up period.

In the year 2000, chloroquine therapeutic efficacy was assessed at two sentinel sites of Kivunge and Micheweni in Zanzibar. Both sites revealed high overall chloroquine treatment failure of around 60%. After this, the Ministry of Health Zanzibar, through the Malaria Control Program, and WHO (AFRO) were interested in getting baseline information on amodiaquine (AQ) and sulfadoxine-pyrimethamine (SP) as potential alternatives. These two antimalarials are commonly used in Zanzibar and mainland Tanzania. The target study population in the efficacy study were children aged 6–59 months attending a health facility. A secondary end point of the trial was to assess hematological response to treatment. The study described here was undertaken from July to August 2001 at Kivunge in Unguja and Micheweni in Pemba, Zanzibar, Tanzania. The results obtained would be used by the Ministry of Health Zanzibar to guide change of policy on first- and second-line antimalarial treatment.

MATERIALS AND METHODS

Study area and population. Zanzibar is situated 30 km from the mainland of East Africa and is off the eastern coast in the Indian Ocean. Zanzibar is made up of two main islands known as Unguja and Pemba, covering an area of 1,666 sq km and 988 sq km, respectively. The main cash crops grown in Zanzibar are cloves, coconut, seaweed, chillies, and copra. Besides subsistence farming, the local people engage in fishing. The largest town and leading port is Zanzibar Town.

Zanzibar has a warm and humid climate with temperatures ranging from 20°C to 36°C. There are two rainy seasons: Masika (March to May) and Vuli (October to November). Malaria transmission occurs throughout the year. However, malaria peak seasons are associated with the long or short rains. According to the 2002 census, the total population of Zanzibar is 984,625. Administratively, the two islands of Unguja and Pemba are divided into five regions: three in Unguja and two in Pemba. Each region is divided into two districts. Each district is in turn subdivided into several constituencies, and Shehias are the smallest administrative structures.

The current study was conducted at the two sentinel sites of Kivunge in North A district and Micheweni in Micheweni district. Some information from the Ministry of Health indicates a steady increase in the number of new cases of malaria reported at PHC Units in Zanzibar.

Screening for malarial parasites and anemia. Screening of children for fever, clinical examination, anemia, malarial parasites, and selection of cases for admission into the study was done up to 1 week before closure of study. Axillary body temperature of all children aged 6–59 months, attending the health facility, were measured with an electronic thermometer. Children found with a history of fever and/or fever (axillary temperature ≥ 37.5°C) were examined further by a clinician to exclude other febrile illnesses. After explaining study aims, follow-up visits and obtaining verbal consent, children were examined for malarial parasites via Giemsa-stained blood smears and anemia by packed cell volume (PCV) estimation. Thick and thin blood films were prepared in duplicate for each child. One slide was used for quick screening while the other, which was stained for a longer period, was used for repeated counting of parasites. Parasite enumeration against 200 leukocytes was done on thick films using the high-power objective of a microscope. A blood film was declared negative...
after counting of 200 high-power fields. Malarial parasite species confirmation was made on the thin film.

**Clinical examination and selection of cases.** Children found to have *P. falciparum* (2,000–100,000 rings/μL) monoinfection and PCV/μL 15% were randomized to receive either SP or AQ, using a table of random numbers. The trial was conducted as previously recommended, with minor modifications, to include cases with a history of fever in the past 24 hours and an upper limit *P. falciparum* density of 200,000 rings/μL. Previous history of chloroquine use was not among the exclusion criteria as recommended elsewhere.

All medication was given under supervision. Details of the antimalarials used were as follows: Fansidar (Roche, sulfadoxine-pyrimethamine 500/25 mg, Basel, Switzerland, batch no. 3006, manufactured May 2000, expiry May 2005) and amodiaquine (Zenula Laboratories Group SA, malaridose 200 mg base, by Lincoln Pharmaceuticals Ltd, Khatraj, India, batch no. ET-0611, manufactured June 2000, expiry May 2003). Oral amodiaquine (25 mg/kg, given over 3 days) was given to 63 children at Kivunge and 70 at Micheweni study sites. Single dose SP (1.25 mg/kg pyrimethamine + 25mg/kg sulfadoxine) was administered to 64 and 61 children at Kivunge and Micheweni, respectively. Paracetamol was given to all children on the first day of medication. Children were observed for 30 minutes to ensure treatment was repeated in case of vomiting. Mothers were advised to use tepid sponging at home in case of fever.

**Parasitological and clinical follow-up.** Further clinical ex-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kivunge</th>
<th>Micheweni</th>
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<tbody>
<tr>
<td>No. in study</td>
<td>64</td>
<td>61</td>
</tr>
<tr>
<td>Age range (months)</td>
<td>6–55</td>
<td>6–57</td>
</tr>
<tr>
<td>Mean age (months, SD)</td>
<td>25.5 (13.3)</td>
<td>25.5 (13.8)</td>
</tr>
<tr>
<td>Mean weight (kg, SD)</td>
<td>10.5 (2.5)</td>
<td>10.6 (2.2)</td>
</tr>
<tr>
<td>Mean temp. (°C, SD)</td>
<td>38.0 (1.0)</td>
<td>38.0 (1.1)</td>
</tr>
<tr>
<td>Temp. range (°C)</td>
<td>36.1–40.2</td>
<td>36.1–40.0</td>
</tr>
<tr>
<td>Parasite range (rings/μL)</td>
<td>2067–9500</td>
<td>2049–228778</td>
</tr>
<tr>
<td>GMD (ring/μL, 95% CI)</td>
<td>13.183 (10,000, 17,378)</td>
<td>13.183 (9,550, 18,197)</td>
</tr>
<tr>
<td>PCV (%, 95% CI)</td>
<td>29.9 (28.8, 31.0)</td>
<td>30.3 (28.9, 31.6)</td>
</tr>
<tr>
<td>Fever prev. (&lt;37.5°C)</td>
<td>50/64 (78.1%)</td>
<td>41/63 (65.1%)</td>
</tr>
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</table>

SD, standard deviation; GMD, geometric mean density; 95% CI, 95% confidence intervals; PCV, packed cell volume.

**Table 1** Baseline characteristics of children treated with either sulfadoxine-pyrimethamine (SP) or amodiaquine (AQ) for uncomplicated falciparum malaria at Kivunge and Micheweni in Zanzibar in July/August 2001.

**Figure 1.** Trial profile for children randomized to receive either sulfadoxine-pyrimethamine (SP) or amodiaquine (AQ) at Kivunge and Micheweni in Zanzibar in July/August 2001.
The evaluation of results was as recommended elsewhere. Briefly, the evaluation scheme values < 0.05 were considered significant. para-

Evaluation of efficacy results. The evaluation of results was as recommended elsewhere. Briefly, the evaluation scheme values < 0.05 were considered significant. parasitemia and any of the following: development of danger signs or severe malaria on Days 1, 2, or 3; axillary temperature ≥ 37.5°C on Days 2 or 3; Day 3 count ≥ 25% of Day 0 count. 2) Late treatment failure (LTF)—presence of parasitemia between Day 4 and Day 14 and any of the following: development of danger signs or severe malaria; axillary temperature ≥ 37.5°C. 3) Adequate clinical response (ACR)—those not meeting the criteria for ETF or LTF with any of the following: absence of parasitemia on Day 14 irrespective of axillary temperature; presence of parasitemia but axillary temperature < 37.5°C.

All cases were further classified into sensitive (S) and resistant (R) to get an indication of P. falciparum parasitological response. Cases of treatment failure were given an alternative antimalarial. Amodiaquine was used for SP failures, whereas AQ failures were given quinine. Cases of severe malaria and those with danger signs were referred to hospital for quinine therapy and further case management. For ethical reasons, all children with malaria parasitemia on Day 14 were given alternative treatment irrespective of clinical condition.

Data and statistical analysis. Data management and analysis was done using EPI-Info version 6.04b and STATA version 7.0 Statistical Software. Comparison of mean PCV levels used Student’s t test. Proportions were compared by the χ² test. P values < 0.05 were considered significant.

RESULTS

Screening for malarial parasites and anemia. Blood smears taken in the screening process revealed malarial parasite prevalence of 48.6% (191 of 393) and 88.4% (191 of 216) at Kivunge and Micheweni, respectively. The prevalence of malarial parasites observed was significantly higher at Micheweni compared with Kivunge (χ² test, P < 0.001). Malarial parasite species distribution at Kivunge was P. falciparum (187 of 191, 97.9%), P. malariae (1 of 191, 0.5%), and P. ovale (0 of 191, 0%) while P. falciparum and P. malariae were found together in 3 out of 191 (1.6%) of the infections. The distribution encountered at Micheweni was P. falciparum (174 of 191, 91.1%), P. malariae (2 of 191, 0.1%), and P. ovale (3 of 191, 1.6%). Mixed infection at this site was P. falciparum plus P. malariae (8 of 191, 4.2%) and P. falciparum plus P. ovale (4 of 191, 2.1%). Overall fever (axillary temperature ≥ 37.5°C) prevalence at presentation was 60.1% (366 of 609). History of previous antimalarial use was similar between the two sites (N = 23 for each site). Anemia was assessed by packed cell volume (PCV) measurement. PCV estimation in 377 of the children attending Kivunge Cottage Hospital showed a mean PCV value of (32.18%, 95% CI = 31.73%, 32.63%). PCV was measured in 216 children attending Micheweni Cottage Hospital. Mean PCV value found was (27.92%, 95% CI = 27.29%, 28.55%). PCV levels seen at Kivunge were significantly higher than those at Micheweni (One sample t test; t = 10.9846, P < 0.0001). Moderate anemia (PCV < 33%) was seen in 174 (46.2%) and 182 (84.3%) of the children at Kivunge and Micheweni, respectively. The prevalence of severe anemia (PCV < 24%) was 4.2% (16 of 377) at Kivunge and 17.5% (38 of 216) at Micheweni.

Treatment outcome. Baseline characteristics of the study cohort are given in Table 1. Children randomized into the study were 64 (mean age = 25.5, SD = 13.3 months) on SP and 63 (mean age = 25.5, SD = 13.8 months) on AQ at Kivunge. Those randomized at Micheweni were 61 (mean age = 20.6, SD = 10.9 months) in the SP group and 70 (mean age = 22.4, SD = 10.1 months) in the AQ group. Fever (≥ 37.5°C) was present in 78.1% and 65.1% of the initial cohort treated with SP and AQ at Kivunge, respectively. Corresponding figures for Micheweni were 65.5% and 67.1%. Figure 1 gives details of the trial profile. Complete follow-up was not achieved in 11 cases for various reasons (development of danger signs Day 0 = 3, mixed malarial infection = 2, protocol violation Day 0 = 2, development of pneumonia = 3, and loss to follow-up = 1). Table 2 shows data on children with complete follow-up. Successful follow-up to Day 14 was achieved in 62 cases on SP and 59 cases on AQ at Kivunge, while for Micheweni it was 58 on SP and 68 on AQ. Evaluation of treatment outcome showed most cases had good response both clinically and parasitologically. ACR was seen in 87.1% (54 of 62) and 94.8% (55 of 58) of the cases on SP at Kivunge and Micheweni, respectively (Table 2). All treatment failures with SP, at both sites, were ETF. ACR with AQ was 93.2% (55 of 59) and 95.6% (65 of 68) at the above study sites. Total treatment failure (ETF and LTF) observed with SP was 9.2% (11 of 120) and with AQ was 5.5% (7 of 127). Table 3 shows data on parasitological response pattern among the ACR cases. The data revealed that overall, 89.9% (205 of 228) of the ACR cases had sensitive (S) P. falciparum parasites. The remaining 10.1% (24 of 228) cases were resistant to either SP or AQ at Kivunge and Micheweni in Zanzibar in July/August 2001.

Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kivunge (N = 62)</th>
<th>Micheweni (N = 59)</th>
<th>SP (N = 58)</th>
<th>AQ (N = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate clinical response (ACR)</td>
<td>54 (87.1%)</td>
<td>55 (93.2%)</td>
<td>55 (94.8%)</td>
<td>65 (95.6%)</td>
</tr>
<tr>
<td>Early treatment failure (ETF)</td>
<td>8 (12.9%)</td>
<td>1 (1.7%)</td>
<td>3 (5.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Late treatment failure (LTF)</td>
<td>0 (0%)</td>
<td>3 (5.1%)</td>
<td>0 (0%)</td>
<td>3 (4.4%)</td>
</tr>
<tr>
<td>Total failures (ETF + LTF)</td>
<td>8 (12.9%)</td>
<td>4 (6.8%)</td>
<td>3 (5.2%)</td>
<td>3 (4.4%)</td>
</tr>
</tbody>
</table>
(R) at RI to RIII levels. Figure 2 shows Kaplan-Meir survival curves on proportion parasite-free cases during the 14-day period after treatment with either SP or AQ. Despite faster clearance of parasites in the AQ group, especially between Days 3 and 7, overall both drugs seemed similar in their ability to clear parasites, with AQ being marginally better than SP.

**Hematological response.** Table 4 shows a comparison of combined mean PCV levels within drugs and between drugs at baseline and on Day 14 of follow-up. Hematological assessment revealed significant gains in mean PCV levels with both drugs (paired t-test, \( P < 0.0001 \)). There was a gain of 2.45% in the SP group (from 28.43% to 30.88%) while the AQ group gained 3.36% (from 28.17% to 31.53%). However, no significant difference (two-sample t-test, \( P = 0.16 \)) was observed in mean PCV values on Day 14 when the two drugs were compared.

**DISCUSSION**

Although vast data on the response of *Plasmodium falciparum* to chloroquine (CQ) and other antimalarials exists for mainland Tanzania, it is rather scarce for Zanzibar. The Ministry of Health Zanzibar and WHO were interested in getting baseline information on potential alternatives, amodiaquine (AQ) and sulfadoxine-pyrimethamine (SP), after findings of high levels (60%) of CQ treatment failure in year 2000 (Lemnge M and others, unpublished data).

The prevalence of malarial parasites observed during the screening process was significantly higher at Micheweni compared with Kivunge (88.6% versus 48.6%; \( P < 0.001 \)). The higher rates of severe anemia (PCV < 24%) as well as lower PCV levels at Micheweni compared with Kivunge (17.5% versus 4.2% and 27.92% versus 32.18%) might be directly related to the malaria situation at the two sites. The data suggest that malaria transmission at Micheweni is more intensive as compared with Kivunge. The main findings of the current study were very high rates (> 90%) of adequate clinical response (ACR) with AQ at both sites. However, ACR observed in the SP group was slightly lower at Kivunge (87.1%) compared with Micheweni (94.8%). Moreover, a higher rate of AQ parasitological resistance (16.7%; RI–RIII) in the ACR group were encountered at Kivunge compared with Micheweni (6.2%; RI only). This might indicate that amodiaquine is more frequently used at the former site or might be that the parasites were new infections due to the relatively short half-life of this drug. On the other hand, most of the cases of SP parasitological resistance (14.5%; RI/RII) were observed at Micheweni; Kivunge had only 5.6% SP parasitological resistance and was of RI grade. This could be due to the fact that SP use was more common at Micheweni where this drug was being used in combination with quinine for a short 3-day quinine treatment of the management of malaria at the hospital (Ali A, personal communication). Notwithstanding this, the overall treatment failure in the two sites was only 9.2% with SP and 5.5% with AQ, indicating Zanzibar was still in the alert stage. Overall, both drugs seemed similar in their ability to clear parasites, with AQ being marginally better than SP. However, AQ showed a faster clearance of parasites between Days 3 and 7 compared with SP. This could be explained by the fact that LTF was seen in the AQ group only and occurred at both sites (5.1% at Kivunge; 4.4% at Micheweni). This observation suggests early and late recrudescence with AQ was the main cause of treatment failures.
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(we are not certain how many were reinfections, in the absence of PCR data). Furthermore, all treatment failures with SP, at both sites, were ETF. This is of clinical significance because ETF occurs in the first 3 days of follow-up when case management is crucial. Hematological assessment revealed significant (P < 0.0001) gains in PCV levels with both drugs, indicating good response to treatment. However, comparing mean PCV levels on Day 14 revealed no significant difference between the two drugs as indicated by the overlapping 95% CI (SP = 30.9%, 95% CI = 30.2, 31.5; AQ = 31.5%, 95% CI = 30.9, 32.2). This again supports the observation that both drugs had an overall similar parasite clearance with AQ being just marginally better than SP. These two antimalarials have been shown to still be effective in clearing parasites at Kilima in Tanzania and Kibwezi in Kenya. However, it has been observed that in a malaria holoendemic area like Mcheweni, increased SP resistance quickly sets in. The presence of high parasitemia in some of the adequate clinical response group (ACR) is of clinical importance because some of these cases, if left untreated, would become symptomatic later on. This shortcoming in the WHO protocol has now been recognized and modified accordingly. However, treatment of all malaria positive cases with an alternative antimalarial was done at the end of the 14-day follow-up period for ethical reasons as recommended.

In conclusion, this report has provided the Zanzibar Ministry of Health and WHO with an insight into the recent level of SP and AQ treatment failures on the islands of Zanzibar and Pemba. The information has provided baseline data on which appropriate measures required for reviewing antimalarial drug policy in Zanzibar have been taken. Although the data on SP and AQ indicates Zanzibar was in fact in the alert period of changing antimalarial drug policy, observations made elsewhere favor adoption of combination therapy (CT) instead of changing from CQ to another monotherapy. Data provided here and that from the preceding CQ trial were used by the Ministry of Health in reviewing antimalarial drug policy in the isles. Zanzibar has now adopted amodiaquine/artsunate and Coartem (artemether/lumefantrine) as the first- and second-line antimalarial drugs, respectively. Regular monitoring of drug response using 28-day follow-up period has been adopted as part of the National Malaria Control Program. This test includes use of PCR to distinguish recrudescence from reinfection.

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