Sulfadoxine-Pyrimethamine in Treatment of Malaria in Western Kenya: Increasing Resistance and Underdosing†

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Between 1993 and 1999, we monitored the efficacy of sulfadoxine-pyrimethamine in 1,175 children aged <24 months receiving 2,789 treatments for falciparum malaria in western Kenya using a widely deployed age-based dose regimen: infants, 125 plus 6.25 mg (sulfadoxine plus pyrimethamine); children aged 12 to 23 months; 250 plus 12.5 mg. Cumulative treatment failure by day 7, defined as early clinical failure by day 3 or presence of parasitemia on day 7, increased from 18% in 1993 to 1994 to 22% in 1997 to 1998 (P-trend test = 0.20). Based on body weight, the median dose received was 20 plus 1.00 mg/kg, and 73% of the treatments were given at lower than the recommended target dose of 25 plus 1.25 mg/kg. Underdosing accounted for 26% of cumulative treatment failures. After the dose was increased in 1998 (median, 36 plus 1.8 mg/kg), only 4.2% of patients received less than 25 plus 1.25 mg/kg and there was no association with treatment failure. However, the proportion of cumulative treatment failure continued to increase to 27% by 1999 (P-trend test = 0.03). These results raise concern about the longevity of sulfadoxine-pyrimethamine in these settings. Underdosing may have contributed to the rate at which sulfadoxine-pyrimethamine resistance developed in this area. Treatment guidelines should ensure that adequate doses are given from the initial deployment of antimalarials onward.

In the last decade several countries in sub-Saharan Africa have switched or are considering switching first-line treatment of uncomplicated falciparum malaria from chloroquine to sulfadoxine-pyrimethamine (S-P), alone or in combination with other antimalarials. Close monitoring of S-P efficacy will be necessary to assess its durability.

We previously monitored the efficacy of S-P from 1993 to 1997 in children younger than 5 years with acute, nonsevere falciparum malaria in an area of western Kenya with intense malaria transmission. The dose of S-P, which was based on age, was found to be an important predictor of treatment efficacy, explaining a quarter of all treatment failures by day 7 (11). Based on their body weight at the time of treatment, three-quarters of the children received less than the internationally recommended target dose of 25 plus 1.25 mg of S-P (25 mg of sulfadoxine plus 1.25 mg of pyrimethamine) per kg of body weight. Similar age-based S-P dose regimens are widely deployed in sub-Saharan Africa. Underdosing also provides an opportunity for the selection of resistant mutants and has been suggested to play a role in the development of resistance (3). These findings led to a revision of the dose recommendations by the Kenyan Ministry of Health in 1998 (2). Here we describe the results of continued annual surveillance of S-P efficacy at the same study site after the introduction of a new dose regimen for S-P in April 1998 that aimed to reduce the proportion of children receiving less than the target dose of 25 plus 1.25 mg of S-P per kg of body weight. The results are compared to the risk of failure before April 1998.

MATERIALS AND METHODS

Procedures. The site and method have been described in detail previously (1, 10, 11). In short; this treatment study was part of the Asembo Bay Cohort Project, a prospective study on the acquisition of natural immunity to malaria (1). Children enrolled in the Asembo Bay Cohort Project, aged less than 5 years (April 1993 to April 1998) or less than 2 years (April 1998 to April 1999) with uncomplicated falciparum malaria, received a supervised dose of S-P: infants, 125 plus 6.25 mg; children aged 12 to 23 months, 250 plus 12.5 mg. Home follow-up occurred on day 2 or 3 and on day 7, with revisits on day 4 or 8 to 10 if the participant was not at home on the scheduled days. Previous analysis indicated that children with a documented history of S-P intake within the previous month were at a 1.7-fold increased risk of subsequent treatment failure when retreated with S-P (11). Recent S-P use (within 28 days) was therefore introduced as a contraindication for S-P treatment from April 1998 onward. All treatment (Table 1) was given under supervision of study staff, and the quality of S-P was confirmed by high-performance liquid chromatography.

Definitions. Treatment failures and successes were defined using a modified version of the World Health Organization classification system (11, 16). Early clinical failure was defined as either clinical deterioration requiring alternative treatment or persistence of fever on day 2 with pure or mixed falciparum parasites that was greater than the pretreatment density or persistence of any Plasmodium falciparum parasites with fever by day 3 or 4. Parasitological treatment failure was defined as the presence of P. falciparum parasites on days 7 to
10 (referred to as day-7), regardless of the presence of symptoms, or a percent decline in parasitemia by day 2 or 3. Cumulative treatment failure by day 7 was defined as having either an early clinical failure by days 2 to 4 or a parasitological treatment failure by days 7 to 10.

Statistical analysis. The SAS software packages SUDAAN release 8 and SAS version 8.0 (SAS, Inc., Research Triangle Institute, Research Triangle Park, N.C.) were used. Confidence intervals (CI) and $P$ values were corrected for multiple observations per child. The effect of treatment dose on parasitological failure by day 7 was modeled by using multivariate log-binomial regression analysis, adjusting for age and study year, with treatment dose categorized in five groups of 5-/0.25-mg/kg S-P and entered as a nominal variable (Fig. 1). $P$-trend values were obtained from similar models by entering the treatment dose as an ordinal variable, using the same categories. Previous comparison of the sensitivity, specificity, and Youden index scores indicated that 27.5 plus 1.375 mg/kg was the most discriminative threshold concentration, below which an increased risk of treatment failure was observed in children younger than 5 years (11). To define the proportion of treatment failures that could be attributed to treatment doses below this concentration, the attributable risk (or population attributable fraction) was calculated. This was done by calculating $\frac{\text{prevalence} \times \text{RR} - 1}{\text{prevalence} \times (\text{RR} - 1)}$ where RR denotes relative risk and prevalence denotes the proportion of children that received doses lower than 27.5 plus 1.375 mg/kg. For all statistical tests, a two-sided $P < 0.05$ was considered to be significant.

The effects of time on treatment outcome were modeled using log-binomial regression, with the study year entered as an ordinal variable in categories of 2 years and adjusting for age, treatment dose, baseline parasite density, degree of TABLE 1. Characteristics of children and treatment regimens used

<table>
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<tr>
<td>S-P dose regimen in children aged:</td>
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<tr>
<td>0–1 mo</td>
<td>125+6.25 mg (1/4 tablet)</td>
<td>125+6.25 mg (1/4 tablet)</td>
</tr>
<tr>
<td>2–11 mo</td>
<td>125+6.25 mg (1/4 tablet)</td>
<td>250+12.5 mg (1/2 tablet)</td>
</tr>
<tr>
<td>12–23 mo</td>
<td>250+12.5 mg (1/2 tablet)</td>
<td>375+18.75 mg (3/4 tablet)</td>
</tr>
<tr>
<td>Pyrimethamine dose (mg/kg), median (IQR)</td>
<td>1.00 (0.79–1.26)</td>
<td>1.79 (1.58–2.08)</td>
</tr>
<tr>
<td>% &lt; 25 plus 1.25 mg/kg</td>
<td>72.6</td>
<td>4.2</td>
</tr>
<tr>
<td>% &lt; 27.5 plus 1.375 mg/kg</td>
<td>84.9</td>
<td>10.6</td>
</tr>
<tr>
<td>Age (mo), median (IQR)</td>
<td>10.1 (6.1–15.4)</td>
<td>10.3 (5.9–14.3)</td>
</tr>
<tr>
<td>Parasite density, median (IQR)</td>
<td>9,533 (3,000–22,120)</td>
<td>10,240 (5,653–19,893)</td>
</tr>
<tr>
<td>History of chloroquine in past 2 wk, no. (%)</td>
<td>485 (19.4)</td>
<td>46 (15.7)</td>
</tr>
<tr>
<td>HbAS phenotype, no. (%)</td>
<td>349 (15.5)</td>
<td>63 (23.3)</td>
</tr>
</tbody>
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* Internationally recommended target dose of 25 plus 1.25 mg/kg.
* Most discriminative dose which differentiates between treatment failure and success.
* Phenotype missing for 240 treatments before 1 April 1998 and 22 after 1 April 1998.
* IQR, interquartile range.
and 1998 resulted in doses below this threshold. The corresponding proportions after the increase in the dose were 4.2% (<25 plus 1.25 mg/kg) and 10.6% (<27.5 plus 1.375 mg/kg) (Table 1). Between 1993 and 1998, the attributable risk for parasitological treatment failure associated with doses below 27.5 plus 1.375 mg/kg was 26.3% (95% CI, 0.8 to 45.4). There was no relationship between dose and treatment failure after the dose increase. Nevertheless a continued increase in treatment failure risk was observed; between April 1998 and April 1999, 27% of treatments failed by day 7 (Fig. 2).

**DISCUSSION**

This study observed an increase in parasitological treatment failure with S-P treatment within 5 years of its introduction as first-line treatment for uncomplicated falciparum malaria in young children in this study area. The high failure risk observed is consistent with recent reports from a treatment trial in northeast Tanzania (5). Although there was no evidence of increasing high-grade clinical resistance in our study, close monitoring of the children in the Tanzanian study showed that two-thirds of children who failed to clear their parasites by day-7 developed clinical malaria within 4 weeks (5). Failure risk assessed by day-7 is likely to underestimate the degree of resistance in the population, because with slowly eliminated drugs such as S-P, most recrudescences in patients in areas with predominantly low-grade resistance occur more than 14 days after treatment. This is the period required to reach patent parasitemia from low parasite levels with multiplication rates being suppressed by host defenses and residual inhibitory concentrations of the drug (14). These results raise concern about the longevity of S-P as monotherapy in these settings.

Between 1993 and 1998, approximately 50% of the population younger than 5 years was enrolled in the Asembo Bay Cohort Project and received S-P as first-line treatment for symptomatic nonsevere falciparum malaria. Although S-P had been introduced into Kenya as a second-line treatment in 1983, it was not widely available in the study area outside the research setting and accounted for less than 1% of S-P treatments reported by caregivers between 1993 and 1997 (10). This changed by early 1999, when the Kenyan Ministry of Health introduced S-P as the new first-line treatment for uncomplicated malaria in this part of Kenya (2). Thus, most of the increase in parasitological treatment failures for S-P in this area occurred prior to its introduction on a larger scale. Of note also is the relatively high failure risk of 18% in 1993.

Apart from innate resistance of the parasite (4), a variety of other factors can contribute to treatment failure in individual patients, including high initial parasite biomass, low host immunity, and insufficient drug concentrations (15). Under these controlled research settings, the intake of S-P was observed and retreatment took place when vomiting occurred. The quality of the study drug used was confirmed, and parasite densities were within the normal range for young children with mild symptomatic falciparum malaria; these factors are unlikely to explain the observations. The present study suggests that a high proportion of treatment failures could be attributed to the relatively low treatment dose (in milligrams per kilogram of body weight) received by most children. Based on the age-based dose regimen used before April 1998, three-quarters of
the children received less than 25 plus 1.25 mg/kg. Doses below 27.5 plus 1.375 mg/kg, the most discriminative threshold concentration associated with treatment failure in previous analyses (11), explained one-quarter of parasitological treatment failures by day 7. An increase in the dose in April 1998 markedly reduced the proportion of underdosing, but this did not result in a decrease in treatment failures, and the rate of annual increase in failure risk remained unchanged (Fig. 2).

Mathematical modeling based on in vitro and in vivo data for mefloquine (as monotherapy) suggest that initial deployment of lower doses provides an opportunity for the selection of resistant mutants and would be expected to lead more rapidly to resistance than the de novo use of maximal doses (8). Similar considerations are likely to apply to S-P. Resistance to S-P arises from point mutations in the plasmodial dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps) genes (7). The use of S-P is associated with a strong pressure to stimulate infective gametocytemia more than other antimalarials do (12). Thus, the low treatment dose used in the current study of young children from northwestern Tanzania is likely to occur when parasites encounter submaximal concentrations of S-P in blood (3), resulting in persistence and preferential transmission of S-P-resistant parasites. Many young children, such as in our study, have insufficient host immunity to clear these resistant infections (3, 8). Furthermore, S-P is known to stimulate infective gametocytemia more than other antimalarials do (12). Thus, the low treatment dose used in the first 5 years of the study is likely to have contributed to the rate at which the initial S-P resistance was able to develop in the population. The previous study of young children from northwestern Tanzania showed that parasitological treatment failure by day 7 following adequate treatment doses of S-P (≥25 plus 1.25 mg/kg) was due primarily to parasites with three mutations in the dhfr domain (S108N, N51I, and C59R) (5). The existence of these triple-mutant parasites in our study site may explain the lack of a significant effect on treatment failure risk after the dose was increased in 1998.

The age-based dose regimen used until 1998 is still recommended by the majority of medical textbooks in 2003 (11). Underdosing is one of the few controllable determinants of the rate at which antimalarial drug resistance develops. It is critical to ensure that treatment guidelines result in adequate doses at the initial deployment of antimalarials when countries alter first-line treatment for nonsevere falciparum malaria. This is particularly relevant when drugs are deployed as monotherapy and are not protected by the concomitant administration of a companion drug with a different mode of action and resistance (combination therapy). For areas such as western Kenya and northeastern Tanzania, it is time to begin to reconsider the role of S-P prior to the emergence of high levels of clinical failure.

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REFERENCES


