EFFICACY OF CHLOROQUINE, SULFADOXINE-PYRIMETHAMINE, AND MEFLOQUINE FOR THE TREATMENT OF UNCOMPULcATED PLASMODIUM FALCIpARUM MALARIA ON THE NORTH COAST OF PERU

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Abstract. As part of an effort to assess antimalarial drug resistance in Peru, we carried out 14-day in vivo efficacy trials of chloroquine (CQ; 25 mg/kg) and sulfadoxine-pyrimethamine (SP; 25 mg/kg of the sulfadoxine component) for the treatment of uncomplicated Plasmodium falciparum infections at three sites on the northern coast of Peru. Mefloquine (MQ; 15 mg/kg) also was evaluated at one site. The results from all three sites were similar. Of the 53 patients treated with CQ, 58.5% had RII/RIII responses. No RIII failures were observed among the 112 patients who received SP, but 4.5% and 1.8%, respectively, had RII and RI responses. All 33 patients treated with MQ showed a sensitive response. Early treatment failures were observed in 27.1% of the CQ patients but in no patients receiving SP or MQ. Late treatment failures were seen in 59.3% of the CQ patients and 6.4% of the SP patients but in none of those treated with MQ. Based on these findings and because of concern about the potential for development of resistance if SP were used alone, the National Malaria Control Program is planning a change in malaria treatment policy to SP-artesunate combination therapy for this region of the country.

INTRODUCTION

Until the early 1990s, chloroquine (CQ) was the drug of choice for the treatment of uncomplicated Plasmodium falciparum malaria throughout Peru. Beginning in 1993, the country experienced a major resurgence of malaria in the Amazon Basin, followed in 1998 by an outbreak of malaria on the northern coastal plain because of increased rainfall and flooding caused by the El Niño phenomenon.1,2 Because of concern about the possibility of antimalarial drug resistance, the Ministry of Health began a series of in vivo therapeutic efficacy trials in 1998. Initial studies at several sites in the Peruvian Amazon region showed widespread resistance to both CQ and sulfadoxine-pyrimethamine (SP).3–5 and the first-line chemotherapeutic regimens.6 As part of this effort to map the distribution of antimalarial drug resistance and assess the efficacy of first-line drugs and potential alternative therapies for P. falciparum malaria, we conducted 14-day in vivo efficacy trials of CQ, SP, and MQ at three sites on the northern coastal plain of Peru.

MATERIALS AND METHODS

The studies were conducted at the Zarumilla Health Center in the Department of Tumbes and the Bellavista and La Arena Health Centers in the Department of Piura during the malaria transmission season from January–July 1999 (Figure 1). This is an area with unstable malaria; P. falciparum accounts for 10–20% of all cases. The three studies were approved by the Ethical Review Committees of the Instituto Nacional de Salud and the U.S. Centers for Disease Control and Prevention.

The methods used followed the recommendations of the Pan American Health Organization for in vivo antimalarial drug efficacy testing in the Americas with minor exceptions.7 Patients from 2–50 years old with suspected malaria at the three health centers were screened for malaria parasitemia with thick blood smears. For all patients, a medical history was obtained, a brief physical examination conducted, and hemoglobin levels measured on admission. Those with P. fal-
under the supervision of a member of the study staff. Subjects were observed for vomiting for 30 minutes after ingesting the drugs; those who vomited the first dose were retreated with an identical dose. Subjects who vomited twice were dropped from the study. Patients with axillary temperatures $\geq 37.5^\circ C$ were treated with paracetamol.

Patients were asked to return for follow-up medical histories, temperature measurements, and thick blood smears on days 1, 2, 3, 7, and 14. Those who did not return were followed up at their homes. Patients who failed to respond to CQ were treated with SP; SP failures were treated with a 7-day course of quinine plus tetracycline (or clindamycin for children younger than 8).

Thick blood smears were stained with Giemsa and the parasite density calculated by counting the number of asexual parasites per 200 white blood cells, assuming a mean white blood cell count of 6,000/$L$. Each blood smear was independently examined by two microscopists. In the case of a difference in results (positive/negative, species diagnosis, or $> 2$-fold difference in parasite density), the blood smear was examined by a third microscopist. The final parasite density was an average of the densities of the two concordant microscopists. Gametocyte density was estimated by counting the number of gametocytes per 500 white blood cells. A total of 200 oil immersion fields were examined before a blood smear was considered negative.

Standard WHO definitions of parasitologic response were used, except that late RI resistance could not be assessed and was combined with sensitive responses for these 14-day trials. The patient’s therapeutic response was classified according to the Pan American Health Organization’s guidelines for in vivo antimalarial drug efficacy testing. An early treatment failure (ETF) was the development of signs of severe malaria with parasitemia on days 1, 2, or 3; a day 2 parasite density $\geq 100\%$ of day 0; or a day 3 parasite density $\geq 25\%$ of day 0. A late treatment failure (LTF) was the development of signs of severe malaria with parasitemia after day 3, clinical deterioration in the presence of parasitemia, or the reappearance of parasitemia from days 7–14. A patient with an adequate clinical response (ACR) was one who did not fulfill the criteria for ETF or LTF and had negative blood smears on days 7 and 14.

RESULTS

A total of 212 patients were enrolled in the studies at the three sites. The characteristics of these subjects are shown in Table 1. No significant differences were observed at the time of enrollment in terms of age, gender, presence of documented fever (axillary temperature $\geq 37.5^\circ C$), mean duration of illness, history of fever or previous malaria infection, geometric mean parasite density, or mean hemoglobin.

Fourteen subjects (6.6%) were excluded from the analysis. Six moved away from the study area, four received additional antimalarial treatment, two had mixed infections on follow-up, one vomited the study medication twice, and one developed a concurrent infection. All remaining subjects completed their 14-day follow-up: 53 had been treated with CQ, 112 with SP, and 33 with MQ. With the exception of the patient who vomited MQ twice, all other subjects tolerated the drugs well.

The proportion of subjects with RII/RIII resistance to CQ was similar at all three sites: 53%, 58%, and 65% (Table 2). Eight percent, 31%, and 19% of patients were classified as ETFs to CQ. Similarly, little variation was noted by site in the proportion of subjects with resistance to SP at the RII/RIII level, 0%, 10%, and 3%, with no ETFs and only 6% LTFs (Table 3). All 33 patients treated with MQ remained parasite-free throughout their 14-day follow-up. No association was found between subjects’ parasitologic outcome and age, parasite density, initial hemoglobin level, or history of vomiting.

DISCUSSION

Most antimalarial drug efficacy studies in South America have focused on the Amazon Basin, where resistance has...
Response to sulfadoxine-pyrimethamine therapy of strains of *Plasmodium falciparum* from the north coast of Peru, 1999

<table>
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<th>Site</th>
<th>N</th>
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<th>RII</th>
<th>RI (early)</th>
<th>RI (late)/S</th>
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<th>LTF</th>
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<td>53</td>
<td>20.8</td>
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* S, RI, RII, and RIII refer to World Health Organization resistance levels
** ETF = early treatment failure; LTF = late treatment failure; ACR = adequate clinical response

Response to chloroquine treatment of strains of *Plasmodium falciparum* from the north coast of Peru, 1999

<table>
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REFERENCES