

Short Report: Surveillance for Adverse Drug Reactions to Combination Antimalarial Therapy with Sulfadoxine-Pyrimethamine plus Artesunate in Peru

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Abstract. In 2001, Peru changed its treatment policy for uncomplicated *Plasmodium falciparum* malaria on the northern Pacific Coast to sulfadoxine-pyrimethamine with artesunate (SP-AS). Because Peru was the first country in the Americas to adopt this combination therapy, we established a surveillance system in the region to assess the frequency of new or worsening symptoms after starting therapy. Over a period of two years, 1,552, or approximately two-thirds of all patients with uncomplicated *P. falciparum* malaria who had received SP-AS on the northern coast were followed up. Of these, 8.8% reported at least one adverse effect, with the most common being vomiting, nausea, headache, abdominal pain, dizziness, and fever; no severe adverse effects related to SP-AS therapy were identified. Treatment of uncomplicated malaria with SP-AS was associated with a low frequency of mild adverse effects in Peru, and therefore should be considered as a first-line therapy in areas of the Americas where SP efficacy is still high.

In recent years, increasing drug resistance has caused many countries to change their policies for treatment of uncomplicated *Plasmodium falciparum* malaria from traditional monotherapies to artemisinin-based combination therapy, as recommended by the World Health Organization.¹ In November 2001, Peru changed the first-line treatment for uncomplicated *P. falciparum* malaria in the Departments of Tumbes and Piura on its northern Pacific coast from sulfadoxine-pyrimethamine (SP) alone to a combination of oral SP (25 mg/kg based on the sulfadoxine component) as a single dose plus oral artesunate (AS), 4 mg/kg/day for three days. SP-AS therapy was implemented after an initial safety and efficacy study of 94 patients showed no severe adverse events (SAEs), but mild adverse reactions were more common in the SP-AS group than in SP alone group.² Although tolerability of this drug combination was supported by studies from Africa and Asia where no SAEs had been documented,^{3–5} there was concern regarding the applicability of those findings to malaria in the Americas where Peru was the first country in the region to adopt SP-AS. Therefore, we designed a study to investigate the incidence of serious, unknown, or infrequent adverse reactions to SP-AS therapy in the northern coast region of Peru.

Surveillance for adverse reactions was conducted in the Departments of Piura and Tumbes on the northern Pacific Coast of Peru where the patient population is of mestizo background (Figure 1). We selected 27 of the 386 health centers in the region that had reported the highest number of *P. falciparum* malaria cases during the preceding two years. The study protocol was reviewed and approved by Naval Medical Research Center Institutional Review Board (Protocol no. 31564) and the Instituto Nacional de Salud Ethics Committee (INS-CE-No. 026-2001).

A total of 1,658 patients with a microscopically confirmed, uncomplicated *P. falciparum* malaria infection sought treatment at one of the 27 health facilities from June 2002 through June 2004. Of these patients, 1,552 with *P. falciparum* malaria who had received SP-AS were enrolled. These patients rep-

resent 65.5% (1,552 of 2,369) of all SP-AS treatments dispensed in the Departments of Piura and Tumbes during that two-year period. The remaining 106 *P. falciparum* patients received some other antimalarial therapy, usually quinine plus clindamycin. We excluded 25 women from the study who were pregnant. Pregnancy tests are not routine in the health clinics prior to administration of antimalarial therapy but according to the Peruvian national treatment policy for malaria, pregnant women who have been diagnosed with *P. falciparum* malaria are mandated to receive quinine and clindamycin. Table 1 provides detailed information on 1,265 of the 1,552 patients enrolled in the study population with regards to age, sex, and nature of malaria episode.

Patients were treated with SP-AS under direct observation on days 0, 1, and 2, and were asked to return for follow up on days 7 and 14. During each visit, trained health care workers asked the patients about new or worsening symptoms after initiation of SP-AS therapy. Patients who reported that they had experienced complications provided a written informed consent and answered questions about additional symptoms. Known or potentially serious illnesses or conditions and/or any hospitalization occurring after initiation of SP-AS therapy were classified as a possible SAE. All unusual health related complaints or symptoms signifying possible SAEs were investigated intensively by a study physician, including detailed histories, physical examinations, and laboratory and pertinent imaging studies, with appropriate specialty referrals. We did not determine drug efficacy of this combination therapy during this study because it had been determined.²

One hundred thirty-seven patients (8.8%) complained of new or worsening symptoms, most of which were mild, did not require discontinuation of SP-AS therapy, and resolved without additional treatment. Fifty-five (3.5%) reported vomiting, 47 (3.0%) nausea, 39 (2.5%) headache, 27 (1.7%) abdominal pain, 27 (1.7%) dizziness or ataxia, 16 (1.0%) fever, 14 (0.9%) malaise, and 10 (0.6%) other signs or symptoms. There were no deaths during follow up. Three patients were admitted to a hospital after beginning treatment with SP-AS and were classified as having possible SAEs. One patient had a syncopal episode with and a chest radiograph indicated signs of congestive heart failure. Further discussion with the patient found that she had dyspnea on exertion for and pe-

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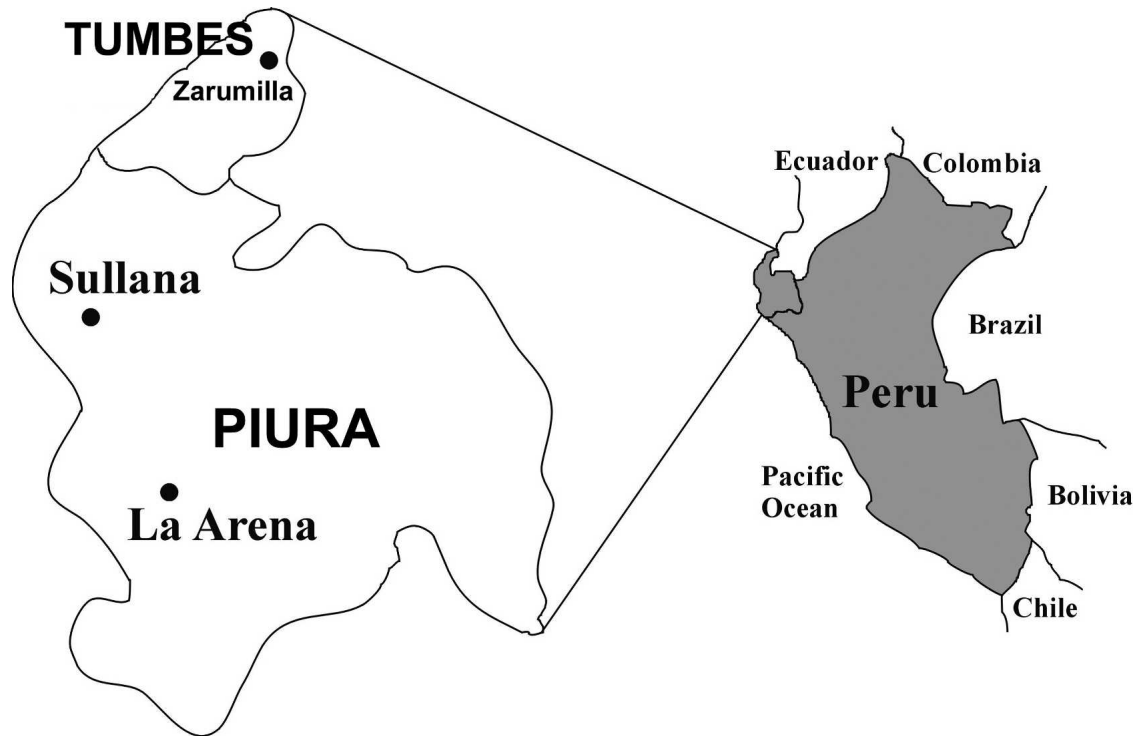


FIGURE 1. Map of the northern coastal region of Peru showing the departments where the 27 health facilities are located.

ripheral edema for 2–4 months before contracting malaria. The second patient was diagnosed with acute pyelonephritis as determined by a positive urine culture. The third patient had a severe case of acute otitis media as indicated by high fever, nausea and vomiting, and bloody right ear discharge. All three patients had symptoms and evidence of other conditions before or at the time diagnosis of malaria was made and each recovered after appropriate treatment. None of their illnesses were considered to be related to SP-AS therapy.

The percentage of adverse reactions seen in this study (8.8%) is less than that reported during drug efficacy trials among children in Gambia where Doherty and others³ and von Seidlein and others⁶ reported a prevalence of AEs of 30% and 55.2%, respectively. In Uganda, Dorsey and others reported malaise in 38% of children receiving SP alone or SP-AS,⁴ and Obonyo and others reported significantly more AEs among children in Kenya receiving SP-AS (76%) than those receiving SP alone (61%).⁷ Our results are similar to previous reports from Indonesia (8.6%),⁵ several places in Sudan (10–14.9%),^{8–10} and our earlier therapeutic efficacy trial of SP-AS (8.9%) in Peru.² Many of the most commonly reported symptoms in this study (nausea, vomiting, headache, dizziness, and fever) could have been caused by the patients' underlying malaria infection. Although cutaneous reactions to SP are well known,¹¹ only 10 patients had such reactions in this study. We did not observe any severe skin reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, which are more frequent when SP is used as prophylaxis.¹²

No neurologic symptoms other than dizziness or ataxia in 27 patients (1.7%) were reported. Animal studies have demonstrated limited symptomatic and pathologic evidence of neurotoxicity after parenteral administration of high doses of

the oil-based artemisinin derivatives artemether and arteether.¹¹ In contrast, postmortem studies of patients who died of severe malaria while receiving treatment with artemether failed to show neuropathologic changes.¹³ There are several case reports of tremors and ataxia in patients receiving oral artemisinins,^{14,15} but these symptoms could be related to malaria¹⁶ or its sequelae. In addition, 1,100 patients in Thailand have had full neurologic examinations after treatment with an artemisinin drug and no specific pattern of neurologic abnormalities was seen.¹⁷ We did not complete neurologic tests in our patients.

TABLE 1
Demographics of the study population from which surveillance for severe adverse effects was conducted

Characteristic	No. (%)	Adverse reactions, no. (%)	
		Yes	No
Total	1,265* (100)	137 (29)	1,128 (71)
Female	520 (41)	72 (14)	448 (86)
Male	745 (59)	65 (9)	680 (91)
Age, years			
≤ 5	33 (3)	3 (9)	30 (91)
≥ 6	1,230 (97)	134 (11)	1,096 (89)
Unknown	2 (0)	0	2 (100)
Parasite count†			
< 40	247 (20)	26 (11)	221 (89)
+2	225 (18)	23 (10)	202 (90)
1+	343 (27)	21 (6)	322 (94)
2+	396 (31)	58 (14)	338 (86)
3+	47 (4)	9 (19)	38 (81)
4+	1 (0)	0	1 (100)
Missing data	6 (0)	0	6 (100)

* Only 1,265 patients records of 1,552 patients enrolled were available for analysis.
† < = 40 parasites in 100 high-power fields (HPFs); +2 = 40–60 parasites in 100 HPFs; 1+ = 1 parasite per field in 100 HPFs; 2+ = 2–20 parasites per field in 100 HPFs; 3+ = 21–200 parasites per field in 100 HPFs; 4+ = > 200 parasites per field in 100 HPFs.

Although the total number of patients followed up in this study was relatively small, it does represent two-thirds of all uncomplicated cases of *P. falciparum* malaria treated with SP-AS on the northern coast of Peru over a two-year period. Treatment with SP-AS was associated with a low frequency of mild, self-limited adverse reactions in Peru, but we did not find any SAE directly associated with treatment. Consequently, we believe that SP-AS is a suitable alternative for treatment of uncomplicated malaria in areas of the Americas where the efficacy of SP is still high.

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