

EFFICACY OF MEFLOROQUINE AND A MEFLOROQUINE-ARTESUNATE COMBINATION THERAPY FOR THE TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA IN THE AMAZON BASIN OF PERU

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Abstract. In the Amazon Basin of Peru, more than 50% of patients with uncomplicated *Plasmodium falciparum* malaria fail to respond to treatment with chloroquine or sulfadoxine-pyrimethamine. To assist the National Malaria Control Program in identifying an alternative first-line therapy for this region, we conducted a trial of the safety and efficacy of mefloquine (MQ) compared with mefloquine-artesunate (MQ-AS) combination therapy. Patients with uncomplicated *P. falciparum* infections between the ages of 5 and 50 years were randomly assigned to be treated with either MQ (15 mg/kg in a single oral dose) or MQ (15 mg/kg) plus AS (4 mg/kg/day for three days). A total of 98 patients were enrolled and followed for 28 days. None of the 47 patients who received MQ alone or the 51 patients who received MQ-AS combination therapy had recurrences of parasitemia during the 28-day follow-up period. Asexual parasite densities decreased significantly more rapidly and the proportion of patients with gametocytes was significantly lower on days 3–21 in the MQ-AS group than in patients treated with MQ alone. All patients tolerated the medication well. Based on the results of this study and with the objective of slowing the development of resistance, the Peruvian Ministry of Health has decided to revise its malaria treatment policy and recommend combination therapy with MQ-AS as the new first-line treatment of uncomplicated *P. falciparum* malaria in the Amazon region.

INTRODUCTION

Since 1996, several antimalarial drug efficacy studies carried out in the Peruvian Amazon region have demonstrated that more than 50% of patients with uncomplicated *Plasmodium falciparum* malaria who are treated with chloroquine or sulfadoxine-pyrimethamine either fail to clear their parasitemia or have a recurrence of parasitemia within 14 days of initiation of therapy (Navitsky RC, Magill AJ, Stennies GM, unpublished data). As a result of these high failure rates, the Ministry of Health of Peru has decided to change its malaria treatment policy for *P. falciparum* infections in this region. Although mefloquine (MQ) might be considered to be the most appropriate alternative in such situations, it is now generally recommended that MQ should always be used in combination with a second drug to delay the development of resistance and prolong its useful therapeutic lifetime.^{1,2} This recommendation is based largely on experiences in Thailand where strains of *P. falciparum* showed a progressive reduction in sensitivity to MQ when used as monotherapy.³ The drugs most commonly recommended for such combination therapy with MQ are artemisinin and its derivatives, such as artesunate (AS). Since there is currently no experience with the use of any of the artemisinin drugs in Peru, we carried out a trial of the safety and efficacy of MQ plus AS for the treatment of uncomplicated *P. falciparum* infections. Mefloquine monotherapy was evaluated at the same time to provide baseline information on the efficacy that drug in the Peruvian Amazon region.

MATERIALS AND METHODS

Study site. The study was conducted at the Hospital de Apoyo Iquitos and the Moronacocha Health Center in the city of Iquitos, Peru (Figure 1), the largest city in the Peruvian Amazon region (population approximately 350,000), during the peak malaria transmission season of 2000. Both health

facilities draw their patient population from the city and surrounding periurban and rural areas. The study was approved by the institutional review boards of the Centers for Disease Control and Prevention, the U.S. Navy, and the Instituto Nacional de Salud.

Between 1990 and 1997, malaria transmission increased dramatically in the Peruvian Amazon region from fewer than 1,000 cases to more than 100,000 reported cases. Transmission in this area is unstable with a peak from March–August. *Plasmodium vivax* is the predominant species; *P. falciparum* accounts for 10–30% of infections. All age groups are affected and the majority of infections are symptomatic, although severe malaria is quite uncommon. The principal vector is *Anopheles darlingi*.

Patients and procedures. 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.⁴ Sample size was calculated based on an expected rate of treatment failure of 2% in the study population, a precision of 5%, and a 5% level of significance. Patients between 5 and 50 years of age with suspected malaria attending the two health facilities were screened for malaria parasitemia with thick blood smears. Those with *P. falciparum* mono-infections between 500 and 30,000 parasites/ μ L of blood and an axillary temperature $\geq 37.5^{\circ}\text{C}$ and/or a history of fever within the previous 48 hours who gave informed consent were enrolled. Subjects were excluded if they had symptoms or signs of severe malaria, had another cause for their fever, had a history of allergy to either of the study drugs, or were pregnant or had a positive urine pregnancy test result.

Subjects were assigned, using a table of random numbers, to receive MQ monotherapy or combination therapy with MQ-AS. Mefloquine (Mephaquin[®]; Mepha, Ltd., Aesch-Basel, Switzerland) was administered in a single oral dose of 15 mg/kg on day 0. Patients in the MQ-AS group received a similar dose of MQ on day 0 plus AS (Plasmotrin[®]; Mepha,



FIGURE 1. Study site in the Amazon Basin of Peru.

Ltd.) in a dose of 4 mg/kg/day on days 0, 1, and 2. All drug administration was supervised by study staff. Subjects were observed for vomiting for 30 minutes after ingesting the drugs; those who vomited the first dose were re-treated with an identical dose. Subjects who vomited the re-treatment dose were dropped from the study. Patients with axillary temperatures $\geq 37.5^{\circ}\text{C}$ were treated with paracetamol.

Subjects were asked to return to the health facilities for follow-up histories of symptoms and possible adverse drug reactions, including vomiting, rash, pruritis, and neuropsychiatric symptoms, on days 1, 2, 3, 7, 14, 21, and 28. Temperatures were measured and thick blood smears were prepared at the same time. Patients who failed to return were followed-up to their homes.

Thick blood smears were stained with Giemsa and the parasite density was calculated by counting the number of asexual parasites per 300 white blood cells, assuming a mean white blood cell count of $6,000/\mu\text{L}$. Each blood smear was independently examined by two microscopists. In the case of a difference in results (positive/negative; species diagnosis; or $\geq 50\%$ difference in parasite density), the blood smear was re-examined by a third independent microscopist. The final parasite density was an average of the densities of the two concordant microscopists. The 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.

Outcome measures. The subject's parasitologic response to therapy was classified as follows: RIII = a day 2 parasite density $\geq 100\%$ of day 0 or a day 3 parasite density $\geq 25\%$ of

day 0; RII = a positive day 3 blood smear with a parasite density $< 25\%$ of day 0 and a positive day 7 blood smear; RI (early) = a negative day 3 blood smear with the reappearance of parasitemia between days 4 and 14 or a positive day 3 blood smear with a parasite density $< 25\%$ of day 0, and a negative day 7 blood smear with the reappearance of parasitemia between days 8 and 14 inclusive; RI (late) = a negative day 3 blood smear or a parasite density $< 25\%$ of day 0, negative day 7 and 14 blood smears, and the reappearance of parasitemia between days 15 and 28; S (sensitive) = a negative day 3 blood smear or density $< 25\%$ of day 0 with negative blood smears between days 4 and 28.

The patient's therapeutic response was classified as recommended by the World Health Organization and Pan American Health Organization guidelines for *in vivo* drug testing.^{4,5} These were defined as follows. An early treatment failure (ETF) was defined as 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 defined as the development of signs of severe malaria with parasitemia after day 3 or clinical deterioration in the presence of parasitemia, or the reappearance of parasitemia between days 7 and 28. An adequate clinical response (ACR) included subjects who did not fulfill the criteria of ETF or LTF with negative blood smears on days 7, 14, 21, and 28.

Statistical analysis. Data were double-entered. Statistical analyses were carried out using SPSS software (SPSS, Inc., Chicago, IL). Dichotomous variables were compared with chi-square or Fisher's exact tests. The Shapiro-Wilk test was used to test for normality of continuous variables, and the Student *t* test or Mann-Whitney U test was used to compare means. Relative risk was used to evaluate incidence rates.

RESULTS

Of the 3,530 patients with suspected malaria who were screened, 115 were enrolled in the trial. Sixty-nine (60%) were males; their mean age was 26.0 years. Sixty-eight (59.1%) of the subjects had a documented fever (axillary temperature $\geq 37.5^{\circ}\text{C}$) on enrollment and 96% had a history of fever in the previous 48 hours. Subjects had a history of 4.5 ± 2.9 (mean \pm SD) days of fever before they were enrolled. Their geometric mean parasite density was $7,798/\mu\text{L}$.

Ninety-eight (85.2%) of the 115 patients enrolled in the study completed the 28-day follow-up period. Seventeen subjects were excluded from analysis, 10 in the MQ group and 7 in the MQ-AS group. Thirteen of these subjects were lost to follow-up (five on or before day 7, four on day 14, three on day 21, and one on day 28), one took a dose quinine plus clindamycin on day 14, and three had low parasite densities on re-examination of their day 0 blood smears.

The characteristics of the 47 subjects who received MQ monotherapy and the 51 who received MQ-AS combination treatment are shown in Table 1. No significant differences were observed on enrollment in terms of age, sex, presence of documented fever (axillary temperature $\geq 37.5^{\circ}\text{C}$), or history of fever. However, subjects treated with MQ-AS had significantly lower geometric mean parasite densities ($P = 0.039$).

All subjects responded well to therapy, and by day 3 only one (2.1%) of the patients in the MQ group and one (2.0%)

TABLE 1

Characteristics of patients enrolled in a mefloquine (MQ) and MQ-artesunate (MQ-AS) *in vivo* drug efficacy study in Iquitos, Peru, 2000

| Characteristic | MQ (n = 47) | MQ-AS (n = 51) | P |
|----------------------------------------------------|-----------------|-------------------|-------|
| Mean \pm SE age (years) | 28.3 \pm 17.3 | 25.9 \pm 15.7 | NS* |
| Males, % | 59.6 | 56.9 | NS |
| History of fever, % | 97.9 | 94.1 | NS |
| Axillary Temperature \geq 37.5°C (day 0), % | 68.1 | 52.9 | NS |
| Geometric mean parasite density (μ L) (day 0) | 13,370 | 6,840 | 0.039 |

*NS = not significant.

of the patients in the MQ-AS group had fever. Asexual parasitemia decreased significantly faster in the subjects who received combination therapy than in those treated with MQ alone (Figure 2). On day 2, 13 (27.6%) of the patients treated with MQ had negative blood smears compared with 42 (82.3%) of those who had received MQ-AS (relative risk = 2.98, 95% confidence interval [CI] = 1.84–4.81, $P < 0.0001$). By day 3, 35 (74.5%) of the patients treated with MQ had negative blood smears in comparison to 50 (98.0%) of those treated with combination therapy (relative risk = 1.32, 95% CI = 1.11–1.56, $P = 0.0006$). All patients were aparasitemic by day 7. Because of the significant difference in parasite densities on enrollment in the two treatment groups, a sub-analysis was performed in patients with day 0 parasite densities $\geq 10,000/\mu$ L. Once again, on both days 2 and 3, patients treated with MQ-AS were more likely to have negative blood smears than those treated with MQ alone (relative risk = 3.65, 95% CI = 1.56–8.53, $P < 0.001$ and relative risk = 1.34, 95% CI = 1.04–1.72, $P = 0.03$, respectively).

On enrollment, there was no significant difference in the proportion of patients in the two treatment groups who had

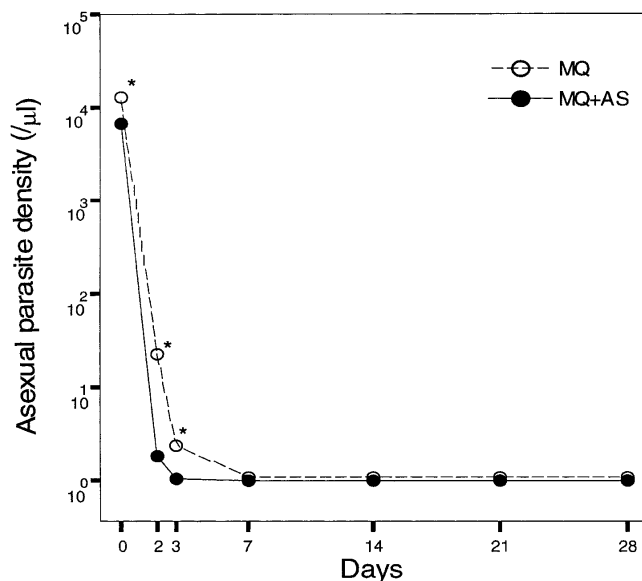


FIGURE 2. Geometric mean parasite density of patients treated with mefloquine (MQ) monotherapy (---) or mefloquine plus artesunate (MQ+AS) combination therapy (—). Points marked with an asterisk indicate a P value ≤ 0.05 .

gametocytes in their blood (6% or 12.8% versus 9% or 17.6%), but the proportion of subjects with gametocytes was significantly lower with combination therapy than with MQ alone on days 3, 7, 14, and 21 (Figure 3). Among patients who had no gametocytes in their blood smears on enrollment, significantly fewer of those treated with combination therapy than MQ alone had gametocytemia on day 3 (7.1% versus 31.7%; $P = 0.01$), day 7 (0% versus 26.8%; $P = 0.001$), and day 14 (0% versus 17.1%; $P = 0.005$).

None of the subjects treated with either MQ monotherapy or MQ-AS combination therapy who completed the trial had a recurrence of parasitemia during the 28 days after treatment. All patients in both treatment groups were classified as having sensitive infections and ACRs. Of the 13 subjects who were lost to follow-up, all but two had cleared their parasitemia and none had a recurrence of parasitemia before they dropped out of the trial.

No severe adverse drug reactions were observed. One 32-year-old subject vomited the first but not the second dose of MQ; a second subject complained of insomnia. No other patients complained of new symptoms or an increase in the severity of pre-existing symptoms after the initiation of therapy.

DISCUSSION

Mefloquine, either alone or in combination with an artemisinin drug, is widely used for the treatment of uncomplicated *P. falciparum* infections in the Brazilian Amazon region.⁶ Although *in vitro* resistance to MQ has been reported from this area since the early 1980s,⁷ only recently have a small number of well-documented cases of RI *in vivo* resistance to a single dose of 15 mg/kg been recorded.^{8,9} In this trial in the Peruvian Amazon region, we found no evidence of resistance to either MQ or MQ-AS; however, at the time the

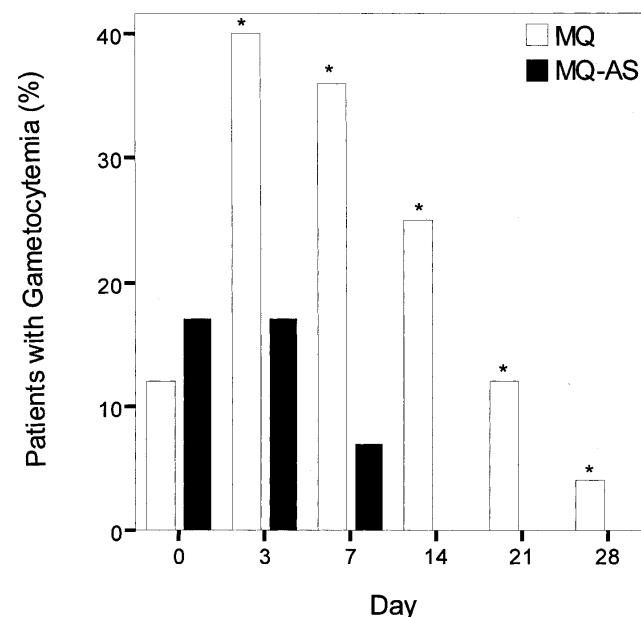


FIGURE 3. Proportion of patients with gametocytes treated with mefloquine (MQ) monotherapy or mefloquine plus artesunate (MQ-AS) combination therapy. Points marked with an asterisk indicate a P value ≤ 0.05 .

study was carried out, artemisinin drugs were not commercially available in Peru, and MQ was only sold in a few pharmacies at a cost of approximately \$4.70 per tablet, making it too expensive for most patients.

We have no explanation for the significantly higher asexual parasite densities at the time of enrollment among those treated with MQ alone, since patients were randomly assigned to the two drug regimens. When this difference was controlled for, however, combination therapy with MQ-AS reduced asexual parasitemia significantly faster than MQ alone, as has been reported from studies in Thailand.¹⁰ In addition, as reported previously, combination therapy with MQ-AS reduced the proportion of patients with gametocytemia significantly faster than MQ alone.¹¹ We did not observe any difference in fever clearance times in patients treated with the two regimens, but the infrequent temperature measurements during the first three days of therapy may account for this.

The rationale for using combination therapy for malaria is similar to that for the treatment of tuberculosis, cancer, and infections with human immunodeficiency virus.² Mefloquine, when used alone, is likely to select resistant parasites because of its long half-life and slow elimination from the blood. Addition of a rapidly acting and highly effective drug, such as artemisinin or one of its derivatives, greatly reduces the probability of selecting parasites that are resistant to both drugs. In Thailand, the addition of AS to MQ therapy for *P. falciparum* infections has been temporally associated with a halt in the steady increase in MQ resistance that had been observed when that drug was used alone.³ Based on these premises and the experiences in Thailand, the World Health Organization now strongly recommends that antimalarial drugs always be used in combination.¹

Although it was initially recommended that in areas with low levels of MQ resistance a dose of 15 mg/kg of MQ should be used in combination with an artemisinin drug,¹ many authorities now believe that MQ should always be used at a dose of 25 mg/kg. This recommendation is based on mathematical modeling of pharmacokinetic and pharmacodynamic data from Thailand, which has shown that initial use of a 15 mg/kg dose provides a greater opportunity for selection of resistant mutations and could thus lead more rapidly to resistance than a dose of 25 mg/kg.¹²

Different commercial preparations of MQ are known to vary in terms of their bioavailability.¹³ A recent study in Thailand comparing Lariam[®] (F. Hoffmann La Roche, Basel, Switzerland) with two other commercial preparations, Mephaquin[®] and Eloquine[®] (Medochemie, Ltd., Limassol, Cyprus) showed that blood levels and the area under the curve with Mephaquin[®] were 50% lower than those with Lariam[®].¹⁴ If the relative bioavailability of Mephaquin[®] to Lariam[®] in South America is similar to that in the Thai study, then our subjects received a dose equivalent to only 7.5 mg/kg. This would mean that strains of *P. falciparum* from the Iquitos area are, at present, highly sensitive to MQ. This finding of 100% efficacy has been confirmed in a smaller 28-day study of 16 patients treated with 15 mg/kg of Mephaquin[®] at another site in the northeastern Peruvian Amazon region, near the borders with Colombia and Brazil (Ruebush TK, unpublished data).

Commonly reported adverse reactions to MQ include anorexia, nausea, and vomiting;¹⁵ vomiting is more frequent in

children less than five years of age.¹⁶ The side effects most commonly observed with the artemisinin drugs are headache, nausea, abdominal pain, vomiting, and occasional diarrhea.¹ In this trial, adverse reactions to both MQ monotherapy and MQ-AS combination therapy were rare. This may have been due to the 15 mg/kg dose, the lower bioavailability of Mephaquin[®], and/or the fact that no children less than five years of age were enrolled in the study.

Based on the high levels of *P. falciparum* resistance to both chloroquine and sulfadoxine-pyrimethamine in the Peruvian Amazon region, the safety and efficacy of MQ-AS demonstrated in this trial, and the goal of preventing or slowing the selection of resistant strains, the Ministry of Health of Peru changed to MQ (25 mg/kg) plus AS as the first-line therapy for uncomplicated *P. falciparum* malaria in most of the Peruvian Amazon region in November 2001.¹⁷ Mefloquine-artesunate therapy will be used in patients of all ages except pregnant women, who will continue to be treated with a seven-day course of quinine plus clindamycin.

It has been shown that the frequency of vomiting associated with MQ can be significantly reduced by administering the drug on the second or third day of the three-day combination treatment.¹⁸ Additionally, the risk of a treatment failure in patients with enrollment parasite densities > 40,000/μL is significantly lower when MQ is administered on the second and third days.¹⁹ In Peru, the decision to administer MQ on the first and second days of the three-day treatment regimen was based largely on practical considerations. In the Amazon Basin, where the population is very scattered, it is not always possible to administer all drug doses under supervision, especially to patients who live far from a health facility or over weekends or holidays when health staff are only available on an emergency basis. To ensure that at least the first day's doses of MQ and AS are ingested, it was felt advisable to begin MQ dosing the first day of therapy.

With implementation of MQ-AS combination therapy for uncomplicated *P. falciparum* infections in the Peruvian Amazon region, Peru has become the first country in the Americas to use this regimen as first-line therapy in their National Malaria Control Program. Plans have already been made to conduct regular surveillance of the efficacy of the new combination therapy regimen through *in vivo* efficacy testing of MQ alone, the component with the longest half-life and, therefore, presumably the most susceptible to selection pressure.²⁰

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REFERENCES

- World Health Organization, 1998. *The Use of Artemisinin and its Derivatives as Anti-Malarial Drugs: Report of a Joint CTD/DMP/TDR Informal Consultation*. Geneva: World Health Organization. WHO Document WHO/MAL/98.1086.
- White NJ, 1998. Preventing antimalarial drug resistance through combinations. *Drug Resist Updates* 1: 3-9.
- Nosten F, van Vugt M, Price R, Luxemburger C, Thway KL, Brockman A, McGready R, ter Kuile F, Looareesuwan S, White NJ, 2000. Effects of artesunate-mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: a prospective study. *Lancet* 356: 297-302.
- Pan American Health Organization, 1998. *Evaluation of the Therapeutic Efficacy of Drugs for the Treatment of Uncomplicated Plasmodium falciparum Malaria in the Americas*. Washington, DC: Pan American Health Organization. OPS/HCP/HCT/113/98.<bok>
- Bruce-Chwatt LJ, Black RH, Canfield CJ, Clyde DF, Peters W, 1986. *Chemotherapy of Malaria*. World Health Organization Monograph Series No 27, Geneva: World Health Organization.
- Ministerio da Saúde, 2001. *Fundação Nacional de Saúde, Manual de Terapêutica de Malária*. Brasília: Brazil.
- de Souza JM, 1983. A phase II clinical trial of mefloquine in Brazilian male subjects. *Bull World Health Organ* 61: 815-820.
- Cardoso BS, Dourado HV, Pinheiro MCN, Crescente JAB, Amoras WW, Baena J, Saraty S, 1996. Estudo da eficácia e tolerância do artesunato oral isolado e em associação com mefloquina no tratamento da malária falciparum não complicada em área endêmica do Pará. *Res Soc Bras Med Trop* 29: 251-257.
- Cerutti C, Durlacher RR, de Alencar FEC, Segurado AAC, Pang LW, 1999. *In vivo* efficacy of mefloquine for the treatment of falciparum malaria in Brazil. *J Infect Dis* 180: 2077-2080.
- Price RN, Nosten F, Luxemburger C, Kham Am, Brockman A, Chongsuphajsiddhi T, White NJ, 1995. Artesunate versus artemether in combination with mefloquine for the treatment of multidrug-resistant falciparum malaria. *Trans R Soc Trop Med Hyg* 89: 523-527.
- Price RN, Nosten F, Luxemburger C, ter Kuile FO, Paiphun L, Chongsuphajsiddhi T, White NJ, 1996. Effects of artemisinin derivatives on malaria transmissibility. *Lancet* 347: 1654-1658.
- Simpson JA, Watkins ER, Price RN, Aarons L, Kyle DE, White NJ, 2000. Mefloquine pharmacokinetic-pharmacodynamic models: implications for dosing and resistance. *Antimicrob Agents Chemother* 44: 3414-3424.
- Weidekamm E, Rüsing G, Caplain H, Sörgel F, Crevoisier C, 1998. Lack of bioequivalence of a generic mefloquine tablet with the standard product. *Eur J Clin Pharmacol* 54: 615-619.
- Na-Bangchang K, Karbwang J, Palacios PAC, Ubalee R, Saengtersilapachai S, Wernsdorfer WH, 2000. Pharmacokinetics and bioequivalence evaluation of three commercial tablet formulations of mefloquine when given in combination with dihydroartemisinin in patients with acute uncomplicated falciparum malaria. *Eur J Clin Pharmacol* 55: 743-748.
- ter Kuile FO, Nosten F, Luxemburger C, Kyle D, Teja-Isavatharm P, Phaipun L, Price R, Chongsuphajsiddhi T, White NJ, 1995. Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3,673 patients. *Bull World Health Organ* 73: 631-642.
- Luxemburger C, Price RN, Nosten F, ter Kuile FO, Chongsuphajsiddhi T, White NJ, 1996. Mefloquine in infants and young children. *Ann Trop Paediatr* 16: 281-286.
- Ministerio de Salud, 1999. *Programa de Control de Malaria y Otras Enfermedades Metaxénicas, Política Nacional de Medicamentos para el Control de la Malaria en el Perú*. Lima, Peru.
- Nosten F, Luxemburger C, ter Kuile FO, Woodrow C, Pa Eh J, Chongsuphajsiddhi T, White NJ, 1994. Treatment of multidrug-resistant *Plasmodium falciparum* malaria with 3-day artesunate-mefloquine combination. *J Infect Dis* 170: 971-977.
- Price RN, Nosten F, Luxemburger C, van Vugt M, Phaipun L, Chongsuphajsiddhi T, White NJ, 1997. Artesunate/mefloquine treatment of multi-drug resistant falciparum malaria. *Trans R Soc Trop Med Hyg* 91: 574-577.
- Watkins WM, Mosobo M, 1993. Treatment of *Plasmodium falciparum* malaria with PSD: selective pressure for resistance is a function of long elimination half life. *Trans R Soc Trop Med Hyg* 87: 75-78.