Effectiveness and Tolerance of Long-term Malaria Prophylaxis With Mefloquine

Need for a Better Dosing Regimen

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To measure the effectiveness and tolerance of long-term malaria prophylaxis with mefloquine, the incidence of *Plasmodium falciparum* malaria and of adverse reactions was compared in Peace Corps volunteers in West Africa who took mefloquine every 2 weeks and in volunteers who took chloroquine phosphate weekly. Mefloquine was only 63% more effective than chloroquine; the monthly incidence of *P falciparum* infections was one case per 100 volunteers who took mefloquine and 2.7 cases per 100 volunteers who took chloroquine. Using daily proguanil (chloroguanide) hydrochloride in addition to chloroquine did not provide additional protection. All mefloquine prophylaxis failures occurred during the second week of the every-2-weeks dosing regimen in volunteers who had used mefloquine for more than 2 months. Blood concentrations of mefloquine were lower during the second week of the alternate-week regimen than during the first week, suggesting that blood levels are too low during the second week to suppress parasitemia. No serious adverse reactions were observed. The results indicate that a dosing regimen of 250 mg of mefloquine weekly should be considered for travelers to areas with chloroquine-resistant *P falciparum* malaria.

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MALARIA has become an important problem for nonimmune visitors to areas with a high risk of infection with drug-resistant *Plasmodium falciparum* malaria. The risk is particularly high for long-term visitors,[1,2] such as missionaries, members of voluntary organizations, and employees of government and private organizations who work in such areas. Since the spread of chloroquine-resistant *P falciparum* in West Africa,[3] the incidence of *P falciparum* among Peace Corps volunteers has increased fourfold in 4 years, from six cases per 100 volunteers in 1986 to 17 cases each in 1987 and 1988, to 24 cases in 1989. Malaria outbreaks occurred among volunteers in Benin in September 1986, followed by sharp incidence increases in Togo, Ghana, Liberia, Mali, and Sierra Leone.[4]

See also pp 317, 383, and 398.

Since 1986, hundreds of confirmed *P falciparum* infections have occurred among volunteers given weekly chloroquine phosphate prophylaxis, with or without concurrent use of daily proguanil (chloroguanide) hydrochloride (Imperial Chemical Industries Ltd, England), especially in West Africa. Because chloroquine therapy, either alone or in combination with proguanil prophylaxis, seemed not to be effective any longer in reliably preventing *P falciparum* malaria, a more effective drug was needed by the Peace Corps.

Mefloquine prophylaxis was documented to be effective and safe for preventing infections with *P falciparum* in 819 semi-immune Thai persons at adult dosing regimens of 180 mg weekly, 360 mg weekly, 360 mg every 2 weeks, 250 mg weekly, and 500 mg every 2 weeks.[5,6] Mefloquine was approved in March 1989 by the Food and Drug Administration for use as an antimalarial agent and was made available to Peace Corps volunteers in Africa in mid-1989. In accordance with the manufacturer's recommendations, the dosing regimen for adult prophylaxis was one tablet of 250-mg mefloquine base every 2 weeks after a loading dosing regimen of one tablet weekly for the first 4 weeks.

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Because no data were available on the use of mefloquine for long-term prophylaxis among nonimmune persons, the surveillance of malaria among Peace Corps volunteers was expanded (1) to measure the effectiveness of long-term mefloquine prophylaxis with the every-2-weeks dosing regimen, (2) to determine the blood concentrations of mefloquine obtained with this dosing regimen, (3) to estimate the blood concentration of mefloquine required to suppress parasitemia, and (4) to evaluate the tolerance of long-term mefloquine prophylaxis.

METHODS

Malaria prophylaxis is mandatory for Peace Corps volunteers in Africa. Volunteers have a choice of one of four chemoprophylactic regimens: mefloquine, weekly 300-mg chloroquine phosphate base, weekly chloroquine with a daily dose of 200 mg of proguanil hydrochloride, or, under unusual circumstances, weekly chloroquine with 25 mg of pyrimethamine and 500 mg of sulfadoxine (Fansidar, Hoffmann-LaRoche Inc, Nutley, NJ). Volunteers considered to be at high risk of infection by the Peace Corps medical officer are encouraged to use mefloquine. However, volunteers cannot be assigned to any one prophylactic regimen group.

As part of the centralized epidemiological surveillance system to monitor health trends among Peace Corps volunteers, data on *P falciparum* infections are provided by Peace Corps medical officers. All cases of *P falciparum* infection are documented by blood smear examination, a detailed history of chemoprophylaxis use is recorded, and, if mefloquine is being used, a whole blood sample is collected to determine the blood concentration of mefloquine. In addition, the medical officers report monthly the number of volunteers using chemoprophylaxis and the drugs being used.[7]

To identify serious adverse events associated with the use of mefloquine, Peace Corps medical officers are required to provide detailed information on each Peace Corps volunteer who seeks medical attention for a suspected serious adverse reaction to any antimalarial drug.

Every 4 months, at the time of the required immune globulin injection, each Peace Corps volunteer completed a questionnaire recording chemoprophylaxis use and any adverse events perceived by the volunteer to be associated with chemoprophylaxis. In addition, a blood sample to determine the blood concentration of mefloquine was obtained at that time from those using mefloquine prophylaxis.

Table 1.—Incidence of *Plasmodium falciparum* Infections Among Peace Corps Volunteers, West Africa, October 1989 to April 1990

Drug Used	No. of Person-Months	No. of Infections	Incidence	Relative Risk (95% Confidence Interval)
Chloroquine phosphate	593	16	2.7	1.00
Mefloquine	1640	17	1.0	0.38 (0.2, 0.76)
Chloroquine and proguanil (chloroguanide) hydrochloride	1175	26	2.2	0.82 (0.44, 1.52)
Chloroquine and pyridimethamine-sulfadoxine	290	9	3.1	1.15 (0.51, 2.51)

Blood samples were obtained by venipuncture and collected in heparinized specimen tubes (Vacutain, Becton-Dickinson, Rutherford, NJ). Whole blood concentrations of mefloquine were determined using high-performance liquid chromatography.[8]

The effectiveness of mefloquine prophylaxis was defined as the reduction of the incidence of *P falciparum* in volunteers using mefloquine compared with that in volunteers using chloroquine. The relative effectiveness of mefloquine prophylaxis was determined by dividing the difference between the incidence of *P falciparum* infections among chloroquine users and mefloquine users by the incidence among chloroquine users. Exact confidence intervals were computed by the method of Fisher.[9] The decline in blood concentrations of mefloquine over time was modeled in a linear regression analysis.

Differences in proportions were analyzed using the χ^2 test and Fisher's Exact Test, and distributions were compared using the Wilcoxon Rank-Sum Test.

RESULTS

The results reported herein are based on observations from October 1989 through April 1990 of Peace Corps volunteers in Benin, Ghana, Guinea, Liberia, Sierra Leone, and Togo, referred to in this study as "West Africa."

Population

Between October 1989 and April 1990, an average of 526 Peace Corps volunteers were stationed in West Africa, for a total of 3698 person-months. Use of mefloquine for prophylaxis increased from 30% of these volunteers in October 1989 to 50% in April 1990, when mefloquine was being used by 264 volunteers. Volunteers began their mefloquine prophylaxis at different times during the 7-month period.

During the study, mefloquine was used for 1640 person-months, chloroquine alone for 593 person-months, chloroquine with daily proguanil for 1175 person-months, and chloroquine with pyrimethamine-sulfadoxine for 290 person-months.

Effectiveness

A total of 17 infections with *P falciparum* were documented among volunteers who took mefloquine, giving an incidence per month of one case per 100 volunteers. During the same time, the incidence of *P falciparum* malaria was 2.7 per 100 volunteers among users of chloroquine (Table 1). Therefore, mefloquine prophylaxis was estimated to be 63% more effective than chloroquine prophylaxis (95% confidence interval, 17% to 84%; $P=.011$). Because volunteers using mefloquine prophylaxis may have been at higher risk of infection than those using chloroquine, it is likely that mefloquine prophylaxis was more effective compared with chloroquine therapy than was estimated. Using daily proguanil or weekly pyrimethamine-sulfadoxine in addition to chloroquine did not provide additional protection (Table 1). The range of the relative risk among users of chloroquine and pyrimethamine-sulfadoxine was due to the small number of person-months in this group.

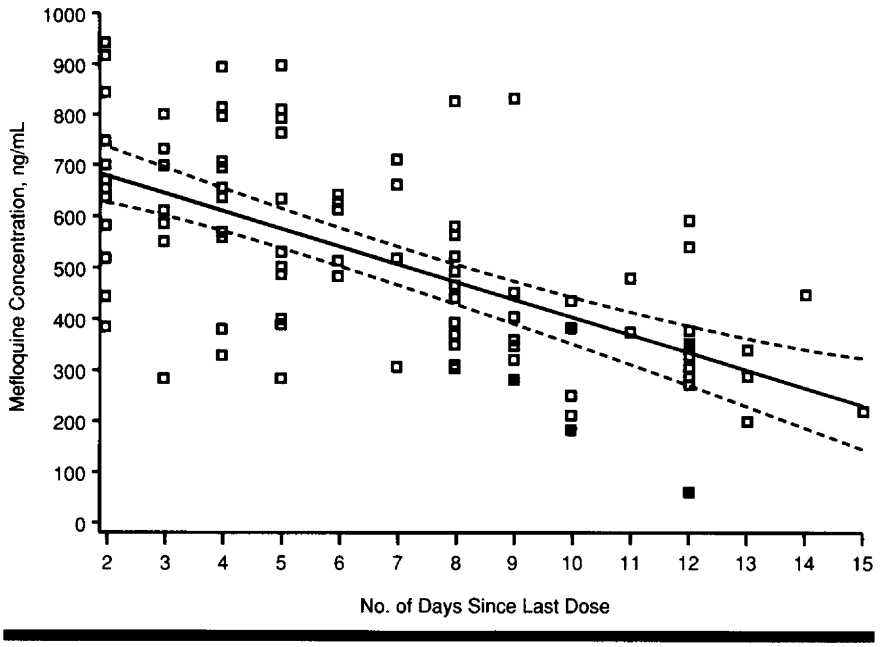
Use of prophylactic drugs and the incidence of *P falciparum* infections for each prophylactic regimen and the overall incidence of *P falciparum* did not differ significantly among the volunteers in the six countries.

All 17 infections in volunteers using mefloquine occurred among those who had used mefloquine prophylaxis for at least 2 months and, therefore, were taking one tablet every 2 weeks. In all infections, the onset of illness occurred at least 8 days (mean, 11.8 days) after taking the last prophylactic dose of mefloquine ($P<.001$). Two infections occurred in volunteers who admitted to missing or delaying one or more doses.

In addition to the 17 infections among volunteers using 250 mg of mefloquine every 2 weeks, infections occurred in two volunteers who had inappropriately used 125 mg of mefloquine weekly after the four initial weekly doses of 250 mg.

Blood Levels of Mefloquine

The concentration of mefloquine in blood samples was determined for 96 volunteers who had recorded the date of



Blood concentrations of mefloquine since last dose. All squares indicate the mefloquine concentrations since the last dose; closed squares, prophylaxis failure; open squares, concentrations in volunteers who did not fail; solid line, regression line; and broken lines, 95% confidence intervals.

Table 2.—Adverse Events Reported by Peace Corps Volunteers

Event	% of Volunteers	
	Mefloquine Therapy (N=231)	Chloroquine Phosphate Therapy (N=67)
Nausea	14.3	28.4
Strange dreams	26.8	26.9
Dizziness	10.8	17.5
Insomnia	12.6	10.4
Weakness	7.4	4.5
Visual problems	6.5	10.4
Diarrhea	3.5	4.5
Total	47.2	49.3

last drug intake, had taken mefloquine for more than 6 weeks, and had taken their last dose at least 2 days before blood samples were drawn. Samples from these volunteers best represent blood concentrations of mefloquine on the every-2-weeks dosing regimen at the steady state. The mean mefloquine concentrations declined gradually, fitting a linear decay regression model (R^2=37%) (Figure). The mean concentration was 603±185 ng/mL during the first week of the every-2-weeks dosing regimen and 406±160 ng/mL during the second week (P=.0001). Blood samples were obtained within 3 days of onset of illness from five volunteers who developed malaria while using mefloquine prophylaxis, and the mean blood concentration of mefloquine was 262±133 ng/mL (range, 62 to 398 ng/mL).

Compliance

Compliance with chemoprophylaxis reported by volunteers on the 4-monthly questionnaires was incomplete; 6% of volunteers using mefloquine and 3% of volunteers using chloroquine admitted to occasionally not taking the prophylaxis (P>.05). None reportedly missed taking prophylaxis frequently. However, the reported compliance with prophylaxis could not be verified independently.

Side Effects

No serious side effects associated with chemoprophylaxis were reported by Peace Corps medical officers. The frequency and type of adverse events reported by volunteers on the 4-monthly questionnaires were comparable among users of mefloquine and users of chloroquine; 109 (47%) of 231 users of mefloquine reported having experienced some adverse event. This compares with 49% of 67 users of chloroquine (with or without concurrent proguanil prophylaxis (P>.05). Events commonly reported included nausea, diarrhea, abdominal pain, dizziness, strange dreams, and insomnia (Table 2).

Few of the events required medical attention. Sixteen mefloquine users and four chloroquine users sought medical evaluation (P>.05), but none of the adverse events was severe.

COMMENT

In this study we determined the effectiveness rather than the efficacy of the every-2-weeks dosing regimen for long-term prophylaxis. The efficacy of prophylaxis depends on the drug concentration necessary to suppress *P falciparum* parasitemia. The efficacy is determined not only by the sensitivity of *P falciparum* parasites to the drug, but also by the blood levels achieved with the amount of drug in each dose and by the dosing frequency. The effectiveness of prophylaxis considers the efficacy and the compliance with the dosing regimen. From the public health viewpoint, the effectiveness of a regimen determines its usefulness. Any differences in compliance among the prophylaxis groups could influence the efficacy but not the effectiveness of prophylaxis.

The comparatively low effectiveness of mefloquine prophylaxis among Peace Corps volunteers was not expected. It was in marked contrast to the 100% efficacy reported in a study of weekly prophylaxis with 250 mg of mefloquine in 110 Thai military personnel. In 38 for whom blood concentrations of mefloquine were determined, the mean was 611±251 ng/mL after 6 weeks, with no significant increase in blood concentrations of mefloquine from 6 to 12 weeks.[6] Among short-term European travelers, the prophylactic effectiveness of weekly doses of 250 mg of mefloquine was 94%; blood concentrations of mefloquine were not determined in that study.[10]

Two factors may have contributed to the low effectiveness of mefloquine prophylaxis. Most probably, the blood levels achieved with the alternate-week regimen were too low during the second week to suppress parasitemia, thereby lowering the efficacy of the drug. Because all prophylaxis failures occurred during the second week of the every-2-weeks dosing regimen, when blood concentrations of mefloquine are lower, the recommended dosing regimen may not be adequate for long-term prophylaxis.

The mefloquine concentrations in blood samples from volunteers who experienced prophylaxis failures were all below 400 ng/mL, suggesting that higher mefloquine concentrations are necessary to suppress *P falciparum* parasitemia in Africa. Slutsker et al[11] found that *P falciparum* infections in young children in Malawi were most likely to persist when the blood concentration of mefloquine was less than 500 ng/mL on the seventh day after therapy.

Second, compliance with mefloquine prophylaxis was not complete. This may be due to difficulties in complying with the every-2-weeks dosing regimen. British health authorities do not recommend mefloquine for long-term prophylaxis because of anticipated difficulties in complying with a dosing regimen that requires changing from weekly dosing to every-2-weeks dosing.[12] In addition, Peace Corps volunteers' long stays abroad may contribute to decreasing compliance. Steffen et al[10] observed that compliance with chemoprophylaxis was lower among long-term travelers than among short-term travelers.

There have been anecdotal reports of *P falciparum* mefloquine treatment failures from West Africa, and in vitro susceptibility tests have suggested that there may be reduced susceptibility to mefloquine in Nigeria.[13,14] However, in vivo and in vitro observations are not adequately correlated to determine if resistance to mefloquine exists in Africa. Furthermore, blood concentrations effective for prophylaxis may not be comparable with those required for therapy of *P falciparum* infections.

No serious adverse reactions were observed among Peace Corps volunteers; mefloquine was tolerated as well as chloroquine (with or without proguanil). These findings are consistent with those of earlier surveys and drug trials of mefloquine prophylaxis. No serious adverse reactions occurred in a total of 18 591 persons: 16 870 European short-term travelers using 250 mg of mefloquine prophylaxis. No serious adverse reactions occurred in a total of 18 591 persons: 16 870 European short-term travelers using 250 mg of mefloquine prophylaxis, and 1721 persons in prophylactic drug trials in Thailand and Malawi with dosing regimens ranging from 180 mg weekly to 500 mg every 2 weeks for periods up to 26 weeks.[10,15-17]

All studies to date confirm that mefloquine is well tolerated when used for prophylaxis; however, monitoring the occurrence of severe adverse reactions is important because such reactions are possible and their association with prophylactic use of mefloquine or their frequency cannot be assessed until the drug has been used widely.[16,18,19] In addition, the nature and impact of the mild adverse events reported with prophylactic use of mefloquine and chloroquine need to be investigated further.

The results of this study have important implications for the prevention of malaria among long-term travelers, temporary residents, and expatriates in areas with drug-resistant *P falciparum* malaria. This now includes all areas with *P falciparum* malaria, except Central America, Hispaniola, North Africa, and the Middle East.[20] Mefloquine is the most effective drug that can be used for long-term prophylaxis, but its effectiveness is compromised by a dosing regimen that requires switching from weekly to bi-weekly administration.

A mefloquine dosing regimen of 250 mg weekly should be considered. This regimen is likely to maintain effective blood levels throughout the period of mefloquine use, and it has been shown to be effective without producing serious adverse reactions in prophylactic trials and among European travelers. In addition, it does not require changing the dosing pattern, thus facilitating compliance. The weekly dosing regimen, therefore, should minimize the factors that now limit the effectiveness of long-term mefloquine prophylaxis.

The Centers for Disease Control has changed the recommended dosing regimen for mefloquine prophylaxis.[21] The new regimen consists of a single dose of mefloquine to be taken *weekly*, starting 1 week before travel. Prophylaxis should be continued *weekly during travel in malarious areas and for 4 weeks after* a person leaves such areas.

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