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Long-term malaria prophylaxis with weekly mefloquine

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The spread of chloroquine-resistant *Plasmodium falpicarum* malaria has led to increased use of mefloquine prophylaxis by US Peace Corps volunteers in sub-Saharan Africa. We compared long-term mefloquine with other drug regimens for effectiveness and tolerance.

The incidence of *Plasmodium falciparum* infections and of adverse reactions was compared in Peace Corps volunteers who took chloroquine weekly, mefloquine weekly, mefloquine every other week, or weekly chloroquine plus daily proguanil. Weekly mefloquine was 94% more effective than chloroquine (95% CI 86% to 97%), 86% more effective than chloroquine plus proguanil (95% CI 67% to 94%), and 82% more effective than prophylaxis with mefloquine when taken every other week (95% CI 68% to 90%). No serious adverse reactions were observed. Mild adverse events were equally frequent in mefloquine users and chloroquine users, and the frequency of these events declined with increasing duration of prophylaxis.

Mefloquine is an effective and well-tolerated drug for prophylaxis of malaria by short-term and long-term travellers.

Lancet 1993; **341**: 848–51.

Introduction

Since 1986, more than 1600 *Plasmodium falciparum* infections have been diagnosed among the approximately 2000 US Peace Corps volunteers in sub-Saharan Africa. These infections have been due in part to the geographical spread of chloroquine-resistant *P falciparum*.[1] Prophylactic mefloquine was made available to these volunteers in September, 1989, because prophylaxis with chloroquine or chloroquine with proguanil was no longer effective. The manufacturer recommended a regimen of 250 mg mefloquine base weekly for the first 4 weeks then to continue with a 250 mg dose every 2 weeks. This regimen was used by Peace Corps volunteers in West Africa from October, 1989, to April, 1990, but resulted in blood concentrations of mefloquine which were too low during the second week after dosing during the every-other-week regimen to suppress parasitaemia.[2] The Centers for Disease Control and Peace Corps therefore recommended that the dosing regimen should be changed to 250 mg mefloquine every week.[3] Surveillance of malaria among volunteers started in October, 1989, and was continued unchanged when the frequency of dosing was increased.

Malaria prophylaxis is mandatory for all Peace Corps volunteers in Africa. Volunteers are encouraged but not obliged to use mefloquine. Three other chemoprophylactic regimens are available: 300 mg chloroquine phosphate base weekly; 300 mg chloroquine weekly with a daily dose of 200 mg proguanil (chlorguanide hydrochloride, Imperial Chemical Industries Ltd, UK); or, rarely, 300 mg chloroquine with 25 mg pyrimethamine and 500 mg sulfadoxine (Hoffman-LaRoche Inc, New Jersey, USA) weekly.

We compare the relative effectiveness of weekly mefloquine prophylaxis with mefloquine every 2 weeks, with weekly chloroquine, and with weekly chloroquine plus daily proguanil. We also estimate the prophylactic effectiveness of varying mefloquine blood concentrations and assess the tolerance of mefloquine when used for long-term prophylaxis.

Methods

Estimates of the effectiveness of malaria prophylaxis are based on observations from October, 1989, to May, 1992, of Peace Corps volunteers in Benin, Ghana, Guinea, Liberia, Sierra Leone, and Togo ("West Africa"). The risk of *P falciparum* infection for volunteers in West Africa was uniformly high. Estimates of the tolerance of chemoprophylaxis are based on a study of 1322 volunteers throughout sub-Saharan Africa.

Blood was taken for a blood-film examination and a detailed prophylaxis history from each volunteer infected with *P falciparum*. If the volunteer had used prophylactic mefloquine, whole-blood concentration of the drug was determined by high-performance liquid chromatography.[4] The number of volunteers who used each prophylaxis regimen was reported by the Peace Corps medical officers each month.

Two methods were used to measure the incidence of side-effects associated with prophylaxis. First, the medical officers provided detailed information on each volunteer who sought medical attention for a serious suspected adverse reaction to antimalarial drugs. Second, every 4 months (at routine immune globulin inoculation) each volunteer completed a questionnaire on chemoprophylaxis compliance and any suspected drug-related event. Between November, 1989, and November, 1990 whole-blood mefloquine concentration was also determined (as above).

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The effectiveness of mefloquine prophylaxis was defined as the reduction of the incidence of *P falciparum* in mefloquine users compared with that in volunteers who used other regimens. The relative effectiveness of mefloquine was calculated by dividing the difference between the incidence of *P falciparum* infections among mefloquine uses (I_m) and users of other drugs (I_o) by the incidence among users of other drugs ($[I_o-I_m]/I_o = 1$-relative risk). Exact confidence intervals (CIs) were calculated by the method of Fisher.[5]

Probit analysis based on the prophylaxis failure risks at different blood concentrations of mefloquine was used to estimate the probability of prophylactic effectiveness at different drug concentrations. Differences in proportions were analysed with χ^2 and Fisher's exact tests, and distributions of continuous variables were compared by Wilcoxon's rank-sum test.

Results

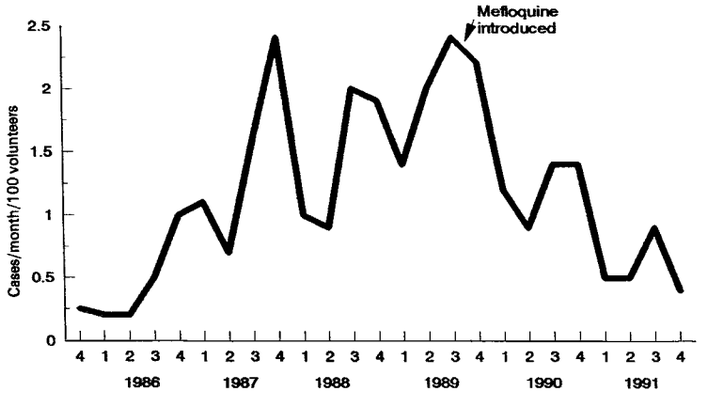
Effectiveness

Between October, 1989, and May, 1992, an average of 421 Peace Corps volunteers were in West Africa for a total of 13 487 person-months. Between October, 1989, and November, 1990, melfoquine every 2 weeks was used in West Africa for 3328 person-months. Weekly mefloquine was used between December, 1990, and May, 1992, for a total of 6230 person-months (table I). Between October, 1989, and November, 1990, 45 *P falciparum* infections were diagnosed in volunteers using mefloquine every 2 weeks—ie, an incidence of 1·4 cases per 100 volunteers per month. The monthly incidence of infections was 3·1 per 100 volunteers among users of chloroquine alone (table I). Mefloquine prophylaxis used every other week was thus estimated to be 56% more effective than chloroquine prophylaxis (95% CI 29% to 73%, p = 0·0006). Mefloquine every 2 weeks was 37% more effective than prophylaxis with chloroquine and proguanil (95% CI 3% to 59%, p = 0·03).

The monthly incidence of *P falciparum* infections between December, 1990, and May, 1992, is shown in table I. Prophylaxis with weekly mefloquine was 94% more effective than prophylaxis with chloroquine (95% CI 86% to 97%, p < 0·0001) and 86% more effective than prophylaxis with chloroquine plus proguanil (95% CI 67% to 94%, p < 0·0001). The addition of daily proguanil to weekly chloroquine did not significantly increase the effectiveness of chloroquine during either time period (table I) although there was a trend towards increased effectiveness. Weekly mefloquine was 82% more effective than mefloquine every 2 weeks (95% CI 68% to 90%, p < 0·0001). The wide range of the confidence intervals of the relative risk for users of chloroquine and pyrimethamine-sulfadoxine was due to the small number of person-months in this group.

TABLE I—INCIDENCE OF INFECTIONS

Drug	Person-months	Infections	Incidence (month/100 volunteers)	Relative risk (95% CI)
Oct 1989–Nov 1990				
Chloroquine	844	26	3·1	1
Mefloquine every 2 wk	3328	45	1·4	0·44 (0·27–0·71)
Chloroquine and proguanil	1818	39	2·1	0·70 (0·42–1·14)
Chloroquine and pyrimethamine-sulfadoxine	422	9	2·1	0·69 (0·32–1·48)
Dec 1990–May 1992				
Chloroquine	236	9	3·8	1
Mefloquine weekly	6230	15	0·2	0·06 (0·03–0·14)
Chloroquine and proguanil	574	10	1·7	0·46 (0·19–1·12)
Chloroquine and pyrimethamine-sulfadoxine	35	2	5·7	1·50 (0·32–6·94)



Incidence of *P falciparum* malaria by quarter among Peace Corps volunteers, West Africa, 1986–1991.

Blood samples were obtained within 5 days of diagnosis from 25 of the 60 volunteers who developed malaria while taking mefloquine prophylaxis. Mean (SD) mefloquine blood concentration was 384 (176) ng/mL. The clinical presentation of malaria in these volunteers was mild (one volunteer was symptomless) and there were few parasites in the blood films.

Our probit analysis suggests that 99% prophylactic efficacy can be achieved at a blood mefloquine concentration of about 915 ng/mL, 95% efficacy at a concentration of 620 ng/mL, and 90% efficacy at 462 ng/mL.

Compliance

Compliance with chemoprophylaxis as reported in the questionnaires was not complete. 5% of volunteers who used weekly mefloquine, 6% of volunteers who used mefloquine every 2 weeks, and 10% of volunteers using chloroquine said that they had missed or delayed one or more doses. None said that they had missed chemoprophylaxis frequently but the reported compliance could not be independently verified.

Malaria in Peace Corps volunteers

Use of mefloquine by volunteers increased from 37% in November, 1989, to 76% in January, 1991, and 97% in May, 1992. Two years after the introduction of mefloquine the incidence had declined to a pre-epidemic level (figure).

Side-effects

No serious adverse drug reactions or hospital admissions associated with any chemoprophylaxis regimen were reported. Apart from nausea, the frequency and type of the mild adverse events reported were similar in mefloquine users and users of chloroquine alone (table II). Only 6

TABLE II—SIDE-EFFECTS (%)

Side-effect	Mefloquine (n = 802)	Chloroquine* (n = 520)
Strange dreams	24·7	26·0
Nausea	8·7†	22·1†
Diarrhoea	4·0	2·7
Dizziness	8·4	6·5
Insomnia	9·0	10·0
Weakness	5·2	2·5
Visual difficulties	6·5	7·5
Any event	40·6	45·8

*With or without proguanil. †p < 0·0001.

(1·8%) mefloquine users reported that the adverse events interfered with their daily activities compared with 11 (4·6%) chloroquine users ($p = 0·07$). 52 (15·9%) mefloquine users sought medical advice for adverse events, as did 37 (15·5%) chloroquine users ($p = 0·994$).

A cohort of 152 volunteers who had used mefloquine for prophylaxis for more than one year was analysed for changes of side-effect rates over time. The frequency of reported adverse events among these volunteers decreased with prolonged use of mefloquine from 44% of volunteers who had used mefloquine for less than 4 months to 40% of those who had used mefloquine between 4 and 7 months, 29% of those who had used the drug between 8 and 11 months, and 19% among those who had used mefloquine for more than 1 year (χ^2 for trend $= 25·47$, $p < 0·0001$), these data suggest that the mild symptoms are well tolerated.

Only 7 (0·9%) of 802 volunteers discontinued mefloquine prophylaxis because of adverse events.

Discussion

These results show that weekly mefloquine prophylaxis is a highly effective regimen to prevent *P falciparum* malaria. Weekly prophylaxis with mefloquine is much more effective than dosing with mefloquine every 2 weeks and it is also more effective than prophylaxis with weekly chloroquine or weekly chloroquine and daily proguanil. Our study shows that long-term prophylaxis with mefloquine is well tolerated.

To reduce bias (a potential difficulty in an observational study in which randomisation was not possible) we limited the study to Peace Corps volunteers in 6 West African countries where the incidence of *P falciparum* malaria was uniformly high. The possibility of bias cannot be excluded but it is unlikely that bias can explain the large differences in effectiveness between mefloquine and chloroquine (94%) and between mefloquine and chloroquine with proguanil (86%). The incidence of *P falciparum* malaria was 19-fold greater in volunteers using chloroquine, and 9-fold greater in those using chloroquine with proguanil, than the incidence in users of weekly mefloquine.

Studies among 200 US Army volunteers found a mean steady-state trough plasma concentration of mefloquine after 6 weeks of weekly prophylaxis of 641 ng/mL (212 ng/mL) (B. Schuster, personal communication). From the probit analysis we estimate that this concentration will prevent malaria in West Africa in 95% of people who use mefloquine for prophylaxis.

Resistance to antimalarial drugs when used for prevention of malaria has not been defined as it has been for therapy of malaria thus the prophylactic effectiveness of a drug is usually estimated from its therapeutic effect.[6] Prophylaxis failures are not necessarily due to drug resistance of the parasite; such failures may also be due to an inadequate drug blood concentration, which could result from noncompliance or from variations in drug absorption and elimination.

At first, anecdotal reports of serious side-effects associated with mefloquine prophylaxis caused concern.[7,8] However, verification of a causal relation requires formal investigations, such as cohort or case-control studies.[9] The results of this study and those of a European cohort study of 140 000 travellers who used malaria chemoprophylaxis[10] indicate that prophylactic mefloquine is well tolerated. We know of no evidence that severe neuropsychiatric reactions (convulsions, psychoses) are causally associated with prophylactic mefloquine use; such events occurred with the same frequency (1/13 000) among 53 000 short-term (average 3 weeks) mefloquine users as among 40 000 users of chloroquine for malaria prophylaxis (R. Steffen, personal communication), and there have been no such reactions among Peace Corps volunteers who used mefloquine for up to $2\frac{1}{2}$ years. However, when mefloquine is used for treatment at doses betwen 750 and 1500 mg, such reactions are estimated to occur in between 1 in 215 and 1 in 1754 patients, 10 to 60 times more frequently than with prophylactic use.[11,12]

The self-reported minor adverse events are unlikely to be associated specifically with use of mefloquine, since users of chloroquine with or without proguanil reported the same events at the same frequency as mefloquine users. Also, the frequency of these side-effects declined with continued mefloquine prophylaxis. Such events are frequently experienced by Peace Corps volunteers: a random sample survey of 1242 volunteers around the world found that during a 4-month period dizziness was experienced by 33% of volunteers, unsteadiness by 28%, insomnia by 37%, strange dreams by 48%, and depression by 46% (J. Moore, personal communication). However, the questionnaire methods used in our study and the random sample survey may not be sufficiently specific to identify reliably such subjective adverse events as disturbances in the sleep and dream patterns.

The absence of effective and well-tolerated drugs in the 1980s to prevent malaria resulted in varying recommendations for travel to malarious areas and for various categories of travellers. This inability to offer simple, uniform recommendations was confusing for the medical profession and short-term travellers and expatriates and led to widely varying prevention practices. For instance, 68 different drug regimens were used by European and North American short-term travellers to Kenya and use of chemoprophylaxis by expatriates has varied widely.[13,14,15]

Because mefloquine is highly effective against chloroquine resistant *P falciparum* malaria in Africa and is well tolerated, the recommendations for malaria prophylaxis for short-term travellers and expatriate residents can now be simplified.

Mefloquine is the drug of choice for malaria prophylaxis in Africa. Mefloquine use is contraindicated only for people with a known hypersensitivity to the drug. Several cautions are listed for use of mefloquine by drivers, pilots, machine operators, people on beta-blockers, pregnant women, children who weigh less than 15 kg, and those with a history of neuropsychiatric illness. However, these precautions are based on limited evidence or theoretical concerns. If mefloquine cannot be tolerated, daily 100 mg doxycycline is an effective alternative drug, but it is not recommended for pregnant women and children under 8 years. If neither mefloquine nor doxycycline can be used, chloroquine (with or without proguanil) may be recommended; however, these travellers must be advised of chloroquine's limited effectiveness and therefore how to manage febrile illness. Such travellers are often recommended to carry a drug with them (pyrimethamine/sulfadoxine or halofantrine) for self-treatment if medical attention is not available.[16,17]

Although mefloquine is highly effective in Africa, resistance may develop against this drug. Thus, continued monitoring and detailed documentation of malaria in people who use mefloquine for prophylaxis is essential. Such documentation should include microscopic confirmation of the malaria diagnosis and determination of the mefloquine blood concentration shortly after the onset of symptoms.

The authors thank the Peace Corps volunteers and the Peace Corps medical officers in West Africa, for making the investigation possible, especially Dr Theresa van der Vlugt, Peace Corps Office of Medical Services for her help.

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Population-based study of non-typable *Haemophilus influenzae* invasive disease in children and neonates

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The extent of non-capsulate, non-serotypable *Haemophilus influenzae* (NST) as a cause of serious invasive disease in children has not been fully defined. We describe the epidemiology of these childhood infections from cases identified during a continuing prospective survey of invasive *H influenzae* disease in the Oxford region, UK.

408 strains of *H influenzae* were isolated from cases of invasive disease. 383 (94%) were *H influenzae* type b (Hib), 24 (6%) were NST strains, and 1 was a type f strain. 3 of the NST strains were non-capsulate type b mutants (b^-), but the remaining 21 strains were from the phylogenetically distinct and heterogeneous population of non-capsulate *H influenzae* (NC). 10 of the NC strains were isolated from neonates with sepsis; crude mortality rate was 40%, with an incidence of 4·6 cases per 100 000 livebirths. 11 NC strains were isolated from children after the neonatal period and under 10 years of age, 4 (36%) of which had severe, unrelated, predisposing conditions. The incidence of NC invasive diseases in these children was 0·5 per 100 000 per year. The attributable mortality for these infections was 10%.

Infections due to these *H influenzae* strains are, after the implementation of Hib vaccines, likely to persist and represent a substantial proportion of the serious infections caused by this species.

Lancet 1993; **341**: 851–54.

Introduction

Whereas capsulate *Haemophilus influenzae* type b (Hib) causes serious invasive disease in young children, the importance of non-capsulate, non-serotypable *H influenzae* (NST) is less well established. Although there are numerous reports of children and neonates with NST systemic infections,[1-6] the attack rate, mortality, and pattern of disease in children of different age groups have not been fully described. Furthermore, the relative importance of such organisms may increase because of the general introduction of type b polysaccharide vaccines, which will greatly diminish invasive Hib disease[7,8] but not systemic infection caused by NST or *H influenzae* of other capsular types.

NST strains belong to one of two distinct groups of organisms—non-capsulate *H influenzae* (NC) strains that are phylogenetically distinct and separate from the population of capsulate strains, and non-capsulate derivatives of Hib[9] or possibly other capsulate types. Serotyping will not differentiate between these two groups.

The genetically distinct populations of NC strains and capsulate *H influenzae* types a–f (including their non-capsulate progeny) can be distinguished by various molecular typing methods. Capsule genes are present in capsulate strains or related non-capsulate variants but not in

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