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ADVERSE HEALTH EVENTS AND MALARIA PROPHYLAXIS

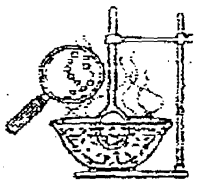
–Hans O. Lobel, MD, MPH

Volunteers and Peace Corps Medical Officers (PCMOs) occasionally voice concerns about the safety and efficacy of mefloquine, a drug used for prevention of malaria in countries with chloroquine-resistant falciparum malaria. Distrust of mefloquine may result in hesitation or refusal to use this drug to prevent malaria and to switch to a less effective drug such as doxycycline or chloroquine. Such action may well lead to more falciparum malaria cases among PCVs and thereby to an increased risk of deaths from malaria. This article reviews the published evidence on the side effects of mefloquine.

At the outset it must be stated that there is no scientific evidence to indicate that mefloquine causes adverse events more frequently than does chloroquine, the drug used for treatment and prophylaxis of malaria for several decades until the emergence of chloroquine-resistant falciparum malaria.

Anecdotal reports of adverse reactions to drugs used for malaria prophylaxis raise concern because such drugs need to be well tolerated. However, it needs to be emphasized that anecdotal reports cannot establish that an adverse event is caused by a drug. To establish a causal relationship, i.e., that the drug causes an adverse reaction, formal scientific investigations are needed, such as cohort or case-control studies.[1] Periodically rumors and anecdotes circulate that mefloquine, used for malaria prophylaxis, can give rise to side effects. Some of the reported events are serious and some are merely unpleasant. These rumors have recently increased as a result of sensational reports on British television, in newspaper articles, and a class action lawsuit against the manufacturer of the drug.

Resistance of falciparum malaria to chloroquine in Africa began in 1978 in Kenya and subsequently spread throughout sub-Saharan Africa, arriving in West Africa in 1986. Malaria infections in Peace Corps Volunteers in West Africa increased rapidly from 8 cases per 100 PCVs in 1986 to 42 cases per 100 PCVs in 1989. Several PCVs experienced 4 to 5 attacks in a year, there were frequent hospitalizations of volunteers suffering from malaria, and several PCVs had to be medically evacuated for treatment of severe malaria during this period.



For comments on malaria prophylaxis from an experienced PCMO, see page 3.

Mefloquine, a drug for prevention and treatment of chloroquine-resistant falciparum malaria, was initially developed under the malaria drug development program of the Walter Reed Army Institute of Medical Research. The drug was made available in 1989 to PCVs in Africa who then could choose between mefloquine or chloroquine (with or without proguanil, a British drug). Intensified malaria surveillance was instituted to document the effectiveness and tolerance of mefloquine as compared with chloroquine. Every 3 months a questionnaire was given to the PCVs asking about the drug(s) used for malaria prophylaxis and any side effects that the PCV attributed to the drug(s). Also a blood sample was collected at that time to determine the concentration of the drug in the blood. It was found that mefloquine was 94% more effective than chloroquine in preventing malaria.[2] The adverse events attributed to mefloquine were compared to those attributed to chloroquine. No differences were found: strange dreams (22.9% in mefloquine users and 26.2% in chloroquine users), insomnia (8.9 and 9.4%), dizziness (8.3 and 6.8%), unsteadiness (6.2 and 2.8%), headache (2.2 and 1.1%). None of these differences was statistically significant. Any CNS events were reported by 31.6% of the mefloquine and 31.9% of the chloroquine users. The adverse events apparently were not serious, and they interfered with daily activities in only 1.8% of mefloquine users and 1.6% of chloroquine users. Medical attention for adverse events was sought by 15.9% of mefloquine users as compared with 15.5% of chloroquine users. Again, there were no differences. Importantly, no case of a serious adverse effect (i.e. psychosis or convulsion) due to mefloquine has been seen in PCVs. The drug has now been used by some 7,000 PCVs for 2-3 years each. There is no evidence that use of weekly mefloquine for several years is associated with an increase in adverse reactions.

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There have been several other cohort studies to assess the effectiveness and tolerance of mefloquine, all confirming the absence of higher health risks among mefloquine users than among users of chloroquine (or a placebo in one study). A Swiss study of short-term travelers to East Africa compared 55,000 users of mefloquine with 40,000 users of chloroquine.[3] Serious adverse events occurred at a frequency of 1:11,000 among the mefloquine and a frequency of 1:14,000 among the chloroquine users, or 1:95,000 person-weeks of use. Among British troops in Kenya the incidence was comparable, 1:81,000 person-weeks of use.[4] These low rates, and their equal frequency among users of mefloquine and chloroquine suggest that such serious adverse events are not drug-associated. A randomized double-blind clinical trial among U.S. Marines in Hawaii not only asked for symptoms, but also included a standardized review of body systems, evaluation of mood states, and a computerized sleep monitor to evaluate sleep quality.[5] The results showed no compromise in function due to dizziness or incoordination. Overall, both mefloquine and chloroquine were well tolerated. Among U.S. troops in Somalia, insomnia was more common among mefloquine than among doxycycline users.[6] Long-term malaria prophylaxis was well tolerated by 2300 Dutch marines in Cambodia.[7] A randomized double-blind placebo controlled cross-over design study among Swissair Trainees compared the effects of mefloquine on performance in a flight simulator and in a computer-based Neurobehavioral Evaluation System, standardized review of body systems and an evaluation of mood states, and documentation of the sleep patterns.[8] No significant differences were detected in any of these tests between mefloquine and placebo. A double-blind randomized placebo controlled study among Indonesian military in Irian Jaya compared mefloquine with doxycycline and placebo. Insomnia occurred less frequently in the mefloquine group than in the placebo group (Ohrt C, personal communication, 1996). A randomized double blind study among British troops in Kenya also found no differences of the frequencies of CNS symptoms between the mefloquine and chloroquine groups (Croft AMJ, personal communication).

What could explain the many anecdotes about adverse effects of mefloquine in the face of the many investigations indicating that the drug is well tolerated when used for prophylaxis? The anecdotal stories focus on neuropsychological events, insomnia, dizziness, strange dreams (some PCVs reported liking them), anxiety, and headache. Such subjective events can occur as the result of stress. These symptoms accounted for half of the consults with PCMOs even before mefloquine was used. For some people travel induces stress and certainly PCVs often encounter stressful situations. Such adverse health events are often attributed to a

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NOTES FROM AN EXPERIENCED AFRICA HAND

One feature of malaria prophylaxis that I have found consistently since I have been associated with expatriates (this includes PCVs and State Department personnel alike) is that there are always complaints about side-effects. When people were on chloroquine alone, they complained that it was making their hair fall out, ruining their libido, stopping them from having a sun tan, and making them go blind. When they were on chloroquine and paludrine they were convinced that the paludrine was ruining their gastrointestinal tract, giving them mouth ulcers and poisoning them, as they equated daily dosing with high toxicity. During the brief period of prophylaxis with chloroquine and Fansidar you would have thought that I was feeding them cyanide.

Now we are in the time of mefloquine. Unfortunately, its very success has bred rumors. The new generation of PCVs and PCMOs has no memory of the desperately sick Volunteers who came down with resistant malaria. They would find it hard to imagine that almost half of our Volunteers were getting sick, one PCV in Kenya died, and the possibility of closing Peace Corps in chloroquine-resistant areas was seriously discussed because we did not have reliable prophylaxis. The arrival of mefloquine at that time was like a wonder drug.

Now malaria is seen relatively rarely so people have forgotten the terrible problems that it created. PCMOs need to realize that expatriates (and humans in general) are going to complain about anything they have to take. The only constant thing about the side effects is that they seem to be the same no matter what people take.

Sheila Waterman, RN, FCM, PA-C, TDY PCMO Guinea-Bissau (PCMO Kenya 1981-85, Togo 1986-94)

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drug on the basis of rumors or hearsay. This may explain why such events are more frequently attributed to mefloquine in some countries than in others. It also needs to be pointed out that any drug, including aspirin, can cause an adverse event in some users.

Despite the scientific evidence indicating that mefloquine is tolerated as well as chloroquine, this may be of little help in determining whether the symptoms in an individual patient could be caused by the drug. If the PCV is switched from mefloquine to another drug to prevent malaria and the symptoms do not disappear, mefloquine is unlikely to be the culprit and the PCV may consider resuming mefloquine prophylaxis. If the symptoms disappear, it can be useful to return to mefloquine prophylaxis to determine if the symptoms reappear. Very often they do not return, suggesting that the symptoms were not related to the use of mefloquine. Even if symptoms are due to mefloquine, the good news is that they always disappear after some time.

It also needs to be pointed out that any drug, including aspirin, can cause an adverse event in some users.

In cases where PCVs attribute adverse health events to mefloquine, the PCMO should assess whether the event is serious enough to require discontinuation of mefloquine. It is the most effective drug available to prevent falciparum malaria, a potentially fatal illness. The PCMO and the volunteer need to be aware that switching to doxycycline is not ideal. Doxycycline requires daily dosing because of its short half life. Therefore, forgetting to take one pill increases the risk of a malaria attack. Conversely, if you miss a weekly dose of mefloquine by one or two days, the mefloquine drug blood concentration will still give effective protection. The experience of U.S. troops who served in Somalia is highly illustrative of this fact where the attack rate among doxycycline users was 5 times higher than among users of mefloquine.[6] This difference was attributed to lack of compliance or missed doses. In addition, doxycycline is associated with several side effects, including phototoxicity, esophagitis, and yeast vaginitis.

Chloroquine (with or without daily proguanil) provides less protection against malaria than doxycycline because of the widespread presence and high level of resistance to chloroquine. The large Swiss study of short-term travelers to East Africa found that weekly chloroquine did not provide any protection.[3] We observed that adding proguanil to chloroquine did not significantly increase the effectiveness of chloroquine.[2]

I will be happy to fax the tabulated summaries of the discussed studies to interested PCMO's. Please call or fax me with your fax number. My telephone number is (770) 488-7790, fax (770) 488-7679.

I am very interested in receiving your comments on the issue of adverse events and malaria prophylaxis. Please send your comments to me by fax or mail (Mailstop F22, CDC, Atlanta, GA 30333).

References

1. Venning GR. Identification of adverse reactions to new drugs. IV-Verification of suspected adverse reactions. BMJ 1983;286:544-547.
2. Lobel HO, Miani M, Eng T, et al. Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993;341:848-51.
3. Steffen R, Fuchs E, Schildknecht J, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. Lancet 1993;341:1299-303.
4. Croft AMJ, World MJ. Neuropsychiatric reactions with mefloquine chemoprophylaxis. Lancet 1996;347:526.
5. Boudreau E, Schuster B, Sanchez J, et al. Tolerability of prophylactic Lariam regimens. Tropical Medicine and Parasitology. 1993;44:257-65.
6. Wallace MR, Sharp TW, Smoak B, et al. Malaria among United States troops in Somalia. Am J Med 1996;100:49-55.
7. Hopperus Buma APCC, van Thiel PPAM, Lobel HO, et al. Long-term malaria chemoprophylaxis with mefloquine in Dutch Marines in Cambodia. J Infect Dis 1996;173:1506-9.
8. Schlagenhauf P, Lobel HO, Steffen R, et al. Tolerability of mefloquine in Swissair trainee pilots. Am J Trop Med Hyg 1996, in press.

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