Suppressive Activity of Mefloquine in Sporozoite-Induced Human Malaria

DAVID F. CLYDE,* VINCENT C. MccARTHY, ROGER M. MILLER, AND RICHARD B. HORNICK

University of Maryland School of Medicine, Baltimore, Maryland 21201

Received for publication 21 October 1975

Mefloquine hydrochloride [WR 142,490; α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol hydrochloride] was tested for suppressive effect on sporozoite-induced malaria in nonimmune volunteers living in an area where malaria is not naturally transmitted. Single doses of 250 mg were given at weekly intervals, 500 mg at intervals of 2 weeks and 1,000 mg at intervals of 4 weeks, to men bitten by 10 to 15 mosquitoes heavily infected with a chloroquine- and pyrimethamine-resistant strain of Plasmodium falciparum. None of the individuals so treated developed infections during the period of drug delivery or during the follow-up period of 60 days. Doses of 250 or 500 mg produced no adverse reactions; mild epigastric discomfort occurred in all three men given 1,000 mg. Sporozoite-induced P. vivax infections were suppressed by single doses of 250 mg of mefloquine given at weekly intervals, but malaria developed after completion of the course. At treatment intervals longer than 1 week, vivax malaria was not suppressed.

MATERIALS AND METHODS

Transmissions were accomplished by use of colonized Anopheles stephensi. Each volunteer receiving mefloquine was bitten by 10 to 15 mosquitoes shown by subsequent dissection to be heavily infected (sporozoite densities in glands, 3+ to 4+). The controls were untreated volunteers bitten separately on each occasion by 10 to 15 mosquitoes from the same batch as those used on the men receiving mefloquine. The parasites used were the Vietnam (Smith) strain of P. falciparum, and the Chesson and El Salvador (Gue.) strains of P. vivax. The Smith strain is resistant to 4-aminooquinolines, pyrimethamine, and chloroguanide (proguanil) and has a diminished susceptibility to quinine (2).

Mefloquine was administered as a single dose in the form of 250-mg tablets or 50-mg capsules, the dose being swallowed under close supervision.

The ethical guidelines of an independent University of Maryland committee were strictly observed in conducting these studies. Details of the care taken in the screening and selection of volunteers, in their daily examination after exposure to infection, and in their clinical maintenance should they develop malaria have been given elsewhere (2). Men inoculated with P. falciparum and not developing malaria were followed for 60 days after the final suppressive dose. Those developing falciparum malaria were treated with quinine after parasitemia was confirmed, and those developing or being exposed to vivax malaria received chloroquine and 14-day courses of primaquine; radical cures were obtained in all instances. Malaria is not transmitted naturally in Jessup, Md., where these studies were undertaken.

RESULTS

Mefloquine as a falciparum suppressive. Mefloquine hydrochloride in doses of 250 or 500 mg was administered at weekly intervals to 14 volunteers, commencing on the day that they were bitten by mosquitoes heavily infected with the Smith strain (Table 1). Some of the men were infected more than once; in particular, volunteer no. 10 was fed on by 70, 60, and 45 infected mosquitoes on days 0, 3, and 6, respectively, the last exposure preceding his final suppressive treatment by only 29 days (Table 1). No side effects were attributable to the treatments, which continued for 7 weeks (volunteer no. 10 for 5 weeks) and provided parasite suppression and suppressive cure in all cases.
All four untreated controls developed malaria within the normal prepatent period.

Mefloquine was also administered at longer intervals. Every 2 weeks, 500 mg was ingested by four men weighing from 59 to 69 kg, the treatment continuing for 6 to 8 weeks without side effects. These men commenced treatment on the day, or 9 days before, they were bitten by mosquitoes heavily infected with the Smith strain. Every 4 weeks, 1,000 mg was ingested by three men weighing from 57 to 75 kg; one man received his first dose on the day that mosquitoes fed on him and his only other dose 4 weeks later, and the other men received their first doses 8 or 14 days after being fed on and then received 2 more doses. Mild epigastric discomfort without vomiting or diarrhea was experienced by all three men shortly following each drug ingestion. None of these men developed malaria during or after treatment with mefloquine.

Mefloquine as a vivax suppressive. Mefloquine hydrochloride in doses of 50, 100, 250, or 500 mg was administered at weekly intervals to 15 volunteers bitten by mosquitoes infected with the Chesson or El Salvador (Gue.) strains (Table 2). All seven untreated controls developed malaria within the normal prepatent period. No side effects were attributable to the treatments. Parasitemia broke through the courses of 50 and 100 mg. It did not appear while 250- or 500-mg doses were being administered but emerged after they were terminated. Some of the men receiving 250 mg of mefloquine were in week 4 of the falciparum study when exposed to vivax infection, as is indicated by their case numbers.

An attempt was made to give mefloquine at longer intervals. With the intention of repeating the dose every 2 weeks, six men weighing from 75 to 89 kg received 250 or 500 mg as a single dose. One man received 250 mg 7 days after being bitten by infected mosquitoes; the remainder were treated on the day of mosquito feeding. All six men together with an untreated control developed parasitemia from 10 to 14 days after exposure to mosquitoes, and the trial was terminated.

**DISCUSSION**

In a study of the effect of a single dose of mefloquine on a multidrug-resistant strain of *P. falciparum* similar to the Smith strain, parasitemia did not develop when nonimmune volunteers were bitten by infected mosquitoes 2 weeks after receiving 1.0 g of the drug; exposure 3 weeks after treatment resulted in the appearance of parasitemia following an extended prepatent period (3). In our study, repetitive doses of 1 g given every 4 weeks, 500 mg every 2 weeks, and 250 mg every week provided
suppression and suppressive cures of mosquito-induced infections with the Smith strain.

As a prophylactic of P. vivax, however, mefloquine is less successful. Suppression occurs during courses of treatment using 250 mg or more once a week, but several weeks after termination of the course parasitemia develops, presumably from relapsing exoerythrocytic forms not affected by the drug. Suppression is not obtained when intervals greater than 1 week elapse between doses.

ACKNOWLEDGMENTS

We are grateful to the volunteers participating in this study and to the Warden and staff of the Maryland House of Correction, Jessup, Md., for their cooperation.

This study was sponsored by the U.S. Army Medical Research and Development Command under contract DA-49-193-MD-2740.

LITERATURE CITED


