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Suppressive Activity of Mefloquine in Sporozoite-Induced Human Malaria[1]

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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.

Mefloquine hydrochloride [WR 142,490; α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol hydrochloride] has been shown to be effective in the owl monkey-human malaria model (4), and human tolerance to the compound and its therapeutic value in clinical malaria have been described (1, 5). In this study, mefloquine has been tested in nonimmune volunteers for suppressive activity against chloroquine- and pyrimethamine-resistant *Plasmodium falciparum* and against *P. vivax*.

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-aminoquinolines, pyrimethamine, and chlorguanide (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.

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TABLE 1. *Prophylactic effect on P. falciparum of mefloquine given weekly*

Dose (mg)	Volunteer[a]	Days of first and last weekly dose	Days of mosquito challenge	Results
250	1. 31, C, 109	0 and 49	0	Suppressive cure
	2. 43, C, 95	0 and 49	0	Suppressive cure
	3. 35, C, 75	0 and 49	0	Suppressive cure
	4. 40, C, 76	0 and 49	0	Suppressive cure
	5. 29, N, 98	0 and 49	0	Suppressive cure
	6. 27, C, 70	0 and 49	0	Suppressive cure
	7. 29, C, 73	0 and 49	0	Suppressive cure
	8. 35, C, 84	0 and 49	0	Suppressive cure
	9. 27, C, 84	0 and 49	0	Suppressive cure
	10. 44, C, 86	0 and 35	0, 3, 6	Suppressive cure
None	11. 28, C, 85		0	Parasitemia on day 9
	12. 40, C, 67		0	Parasitemia on day 10
	13. 36, C, 77		0	Parasitemia on day 10
500	15. 32, C, 120	0 and 49	0 and 4	Suppressive cure
	16. 27, N, 85	0 and 49	0 and 4	Suppressive cure
	17. 34, C, 68	0 and 49	0 and 4	Suppressive cure
	18. 42, C, 73	0 and 49	0 and 4	Suppressive cure
None	19. 33, C, 75		0	Parasitemia on day 10

[a] The number assigned the volunteer is followed by his age (in years), his race (C, Caucasian; N, Negro), and his weight (in kilograms). Volunteers 1 to 13 were exposed to one batch of mosquitoes, and volunteers 15 to 19 were exposed to another.

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 before 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

TABLE 2. *Prophylactic effect on P. vivax of mefloquine given weekly*

Dose (mg)	Volunteer[a]	Days of first and last weekly dose	Days of mosquito challenge	Result: day parasitemia appeared
50	27. 31, C, 69	−7 and 7	0	10
	28. 41, C, 68	−7 and 7	0	10
100	29. 37, C, 76	0 and 7	0	12
	30. 28, C, 77	0 and 7	0	12
	31. 23, C, 80	0 and 7	0	12
250	1. 31, C, 109	−24 and 25	0	83
	8. 35, C, 84	−24 and 25	0	77
	2. 43, C, 95	−21 and 28	0	–[b]
	4. 40, C, 76	−21 and 28	0	147
	7. 29, C, 73	−21 and 28	0	79
	9. 27, C, 84	−21 and 28	0	78
None	14. 27, C, 84		0	9
250	43. 46, C, 95	0 and 49	0	–
	44. 28, C, 77	0 and 49	0	–
None	45. 37, C, 57		0	12
	46. 33, C, 70		0	11
	47. 43, C, 73		0	10
	48. 39, C, 75		0	12
250	39. 32, C, 71	0 and 35	0	–
None	40. 33, C, 75		0	11
500	41. 40, C, 77	0 and 49	0 and 4	–
None	42. 26, C, 72		0	12

[a] The number assigned the volunteer is followed by his age (in years), his race (C, Caucasian; N, Negro), and his weight (in kilograms). Volunteers 1 to 14 were exposed to one batch of mosquitoes carrying E1 Salvador vivax, volunteers 43 to 48 to another batch carrying E1 Salvador vivax, and volunteers 39 to 42 and 27 to 31 to other batches carrying Chesson vivax.

[b] Follow-up was prematurely terminated for administrative reasons, and primaquine was given to volunteer 2 on day 98, 39 on day 36, 41 on day 131, and 43 and 44 on day 59.

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.

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