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Mefloquine (WR 142,490) in the Treatment of Human Malaria

Abstract. *Mefloquine hydrochloride, a new 4-quinolinemethanol, was administered as a single oral dose to 47 volunteers infected with malaria. Treatment resulted in rapid clearance of fever and parasitemia. No recrudescence of parasites was observed after treatment of chloroquine-sensitive infections of* Plasmodium falciparum. *More significantly, in nonimmune persons with chloroquine-resistant infections, 1 gram of mefloquine cured 10 of 12 patients and 1.5 grams cured all 8 patients who received this dose of the drug. The marked activity of a single dose of mefloquine against chloroquine-resistant strains of* Plasmodium falciparum *suggests that this agent may be more useful than currently available drugs are for the treatment of drug-resistant malaria.*

Malaria remains one of the most important health problems in the world today. The emergence of chloroquine resistance in *Plasmodium falciparum*, the most pernicious plasmodial species for man, has resulted in an intensive search for new drugs and the reappraisal of older ones. At present, no completely suitable regimen is available for treatment of patients infected with chloroquine-resistant strains of *P. falciparum* (*1*).

About three decades ago, a large number of 4-quinolinemethanols were investigated for their antimalarial activity in avian malaria models. The agent with the greatest activity, SN 10,275 [α-(2-piperidyl) - 6,8-dichloro-2-phenyl-4-quinolinemethanol], was tested in volunteers infected with the Chesson strain of *Plasmodium vivax* (*2*). Although phototoxic side effects prevented the general use of this compound, it was an effective blood schizonticidal agent with a remarkably long duration of activity. A derivative of this compound, WR 30,090 [α-(dibutylaminomethyl) - 6,8-dichloro-2-(3′,4′ - dichloro)phenyl-4-quinolinemethanol], has since been found to be highly effective in man against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*. This 4-quinolinemethanol showed minimal evidence of phototoxicity but demonstrated a relatively short duration of action (*3*, *4*).

Mefloquine hydrochloride [WR 142,490; α - (2 - piperidyl) - 2,8 - bis(trifluormethyl)-4-quinolinemethanol] is an analog of SN 10,275 and WR 30,090 (Fig. 1). Preclinical studies revealed that this agent was more effective than WR 30,090, had the long duration of action characteristic of SN 10,275, and showed no evidence of phototoxicity (*1*, *5*). On the basis of these findings, studies were initiated to determine the safety and efficacy of a single oral dose of this drug in the treatment of malaria in man, particularly in individuals infected with chloroquine-resistant strains of *P. falciparum*.

During the first phase of these studies, the tolerance and safety of mefloquine were appraised in noninfected individuals (*6*) by a single-dose, double blind design with 19 dose levels rising from 5 to 2000 mg. At each dose level, two persons in the group received the drug and two received the placebo. To evaluate drug tolerance, the following procedures were performed twice before and several times during the 3 weeks after drug administration: interview, physical examination, electrocardiogram, hematocrit, total white blood cell count, white blood cell differential, platelet count, prothrombin time, total serum bilirubin, serum creatinine, serum glutamic oxalacetic transaminase, blood urea nitrogen,

Table 1. Response of 35 nonimmune volunteers infected with *Plasmodium falciparum* to treatment with mefloquine.

Strain of *Plasmodium falciparum*	Dose of mefloquine hydrochloride		No. treated	Asexual parasites mm³ (No.)*	Maximum rectal temperature (°C)	Clearance time (days)		No. cured
	mg	mg/kg				Fever†	Asexual parasites	
Ethiopian (Tamenie)	400	5.4‡ (4.6– 6.2)	2	1,610‡ (1,520– 1,700)	41.5‡ (41.5–41.5)	5.5‡ (5–6)	4.0‡ (3–5)	1
Vietnam (Marks)	400	5.5 (3.9– 7.5)	8	2,195 (240– 8,880)	40.4 (39.8–40.6)	4.1 (2–6)	5.1 (2–7)	1
Cambodian (Buchanan)	400	5.6 (5.2– 5.9)	2	2,835 (2,550– 3,120)	40.3 (40.1– 40.6)	5.0 (4–6)	5.0 (4–6)	0
Ethiopian (Tamenie)	1,000	10.4 (7.7–12.5)	3	810 (520– 1,130)	40.1 (39.4–40.9)	5.0 (4–6)	3.0 (2–4)	3
Vietnam (Marks)	1,000	14.6 (13.6–15.4)	8	3,437 (760– 8,480)	41.0 (40.6–41.6)	5.25 (4–7)	3.1 (3–4)	8
Cambodian (Buchanan)	1,000	13.9 (10.7–17.2)	4	10,090 (740–28,200)	41.2 (40.9–41.3)	4.5 (4–6)	4.75 (4–7)	2§
Cambodian (Buchanan)	1,500	21.2 (16.8–26.2)	8	8,437 (830–18,750)	40.1 (39.1–41.3)	3.5 (2–6)	4.0 (3–5)	8

*Maximum parasite count during the first 48 hours of treatment. †Interval between treatment and the first day of a 48-hour period during which the rectal temperature remained below 38°C. ‡Mean, with range in parentheses. §The individuals who were not cured received 10.7 and 13.2 mg of mefloquine per kilogram and those who were cured received 14.5 and 17.2 mg of the drug per kilogram.

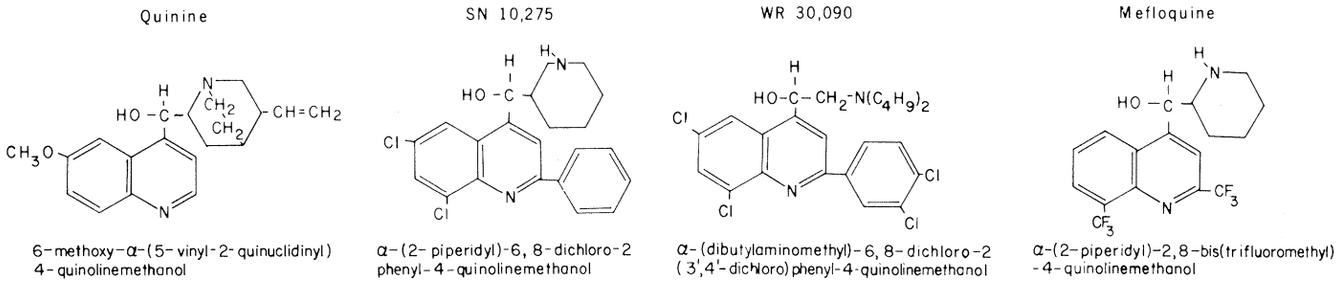

Fig. 1. Structural formulas of SN 10,275, WR 30,090, and mefloquine. Quinine is included for comparison.

alkaline phosphatase, fasting blood sugar, creatinine clearance, and 24-hour urinary protein excretion.

No symptoms, abnormal physical findings, or drug-related laboratory abnormalities occurred through the first 17 dose levels (to 1500 mg). At 1750 and 2000 mg, all four subjects who received the drug reported transient dizziness and nausea within the first 48 hours. However, another group of four volunteers who received 2000 mg of the drug showed no evidence of drug toxicity (*7*). Phototoxicity (*8*) was not observed in any of the 42 individuals who participated in this phase of the study.

During the second phase of these studies, the therapeutic efficacy of the drug was determined in individuals (*6*) infected with malaria. Volunteers were inoculated by the bites of infected mosquitoes (*Anopheles stephensi*) or by the intravenous inoculation of a small amount of washed parasitized red blood cells (*9*). These blood cells for inoculation were obtained only from donors whose serum was negative for hepatitis-associated antigen by radioimmunoassay. These studies involved three strains of *P. falciparum*: the Vietnam (Marks), a strain resistant to chloroquine and amodiaquine and to several folic acid antagonists (*10*); the Cambodian (Buchanan), another multidrug-resistant strain (*1*); and the Ethiopian (Tamenie), a strain sensitive to conventional doses of chlorine, amodiaquine, and pyrimethamine. In addition, limited studies were conducted with the Chesson strain of *P. vivax*; blood-induced infections of this strain are cured by conventional doses of chloroquine, whereas mosquito-induced infections also require administration of primaquine to prevent relapses. Participants were hospitalized at the onset of patent parasitemia and remained under the close supervision of a physician throughout the course of the study. Parasite counts were performed at least daily (*11*). After drug administration, individuals infected with *P. falciparum* were considered cured if there was no recrudescence of parasitemia within 60 days of treatment. Individuals whose infections with the Chesson strain of *P. vivax* were mosquito-induced were considered cured if no relapse of parasitemia was observed within 10 months after treatment; those whose infections were blood-induced were considered cured after a follow-up period of 60 days. The same procedures that were used in the first phase of the study for detection of drug intolerance were followed during this phase.

Thirty-five nonimmune (*12*) volunteers infected with *P. falciparum* were treated with a single oral dose of mefloquine between 2 and 10 days after the onset of patent parasitemia (Table 1). Administration of 400 mg of the drug to 12 persons resulted in clearance of fever and parasitemia in all of them, but only two were cured of their infections. Administration of 1000 mg of the drug cured all three persons infected with the Ethiopian strain and all eight persons infected with the Vietnamese strain. Although clearance of asexual parasites was rapid in all four individuals infected with the Cambodian strain, two of them had a recrudescence of parasitemia 30 and 35 days after treatment with 1000 mg of mefloquine. Within 1 to 3 days, they were treated with another dose of 1000 mg of the drug; one was cured and one was not. When eight additional persons infected with the Cambodian strain received a single dose of 1500 mg of mefloquine, all of them were cured by treatment with this higher dose.

Table 2. Response of seven partially immune volunteers infected with *Plasmodium falciparum* to treatment with mefloquine.

Strain of *Plasmodium falciparum*	Dose of mefloquine hydrochloride (mg)	No. treated	No. cured
Vietnam (Marks)	250	2*	0
Cambodian (Buchanan)	250	1	1
Ethiopian (Tamenie)	500	1	1
Vietnam (Marks)	500	4†	4
Cambodian (Buchanan)	500	1	1

*These two individuals were treated later with 500 mg of mefloquine (see other footnote). †Two of the individuals were treated during a recrudescence of parasitemia, 43 and 45 days, respectively, after initial treatment with 250 mg of mefloquine.

In addition, seven partially immune (*12*) volunteers infected with *P. falciparum* were treated between 35 and 134 days after onset of patent parasitemia (Table 2). Recrudescence of parasitemia was observed in two of the three individuals who received 250 mg of mefloquine. Both of them, in addition to four other individuals, were cured by treatment with 500 mg of the drug.

Five partially immune volunteers infected with the Chesson strain of *P. vivax*, treated between 47 and 135 days after onset of patent parasitemia, showed rapid clearance of parasites after treatment. In two individuals with blood-induced infections, one was cured by treatment with 400 mg of mefloquine and the other by treatment with 1000 mg. In three individuals with mosquito-induced infections, parasitemia reappeared in two participants 14 and 24 days after treatment with 400 mg of mefloquine and in the third participant 68 days after treatment with 1000 mg. These individuals were subsequently cured of their infections by a standard course of chloroquine and primaquine (*13*). The results suggest that mefloquine may be useful in terminating acute attacks of vivax malaria but that, in addition, supplemental treatment with a tissue schizonticidal drug, such as primaquine, will be necessary to achieve radical cure.

Additional studies conducted at this laboratory indicate that a single dose of mefloquine administered to man has a prolonged antimalarial activity against *P. falciparum*. A method for chemical analysis of mefloquine in biological fluids is not available and, consequently, a modification of our in vitro system (*14*) was used to assess the antimalarial activity of the drug in serum. Significant blood schizonticidal activity was observed in serum samples collected from individuals 28 days after they had received 1000 mg of this drug. Furthermore, uninfected volunteers who were given a single dose of the drug failed to develop malaria when they were bitten 14 days later by mosquitoes infected with *P. falciparum* (*15*).

Although a number of different drugs or drug combinations are available for the treatment of chloroquine-resistant infections of *P. falciparum*, most of them must be administered for a period of 5 to 14 days. Shorter courses of treatment usually consist of the combination of a dihydrofolate reductase inhibitor, such as pyrimethamine, and a long-acting sulfonamide, such as sulfadoxine or sulfalene. Single-dose treatment with such combinations has been effective, but some patients do not respond adequately to these drug regimens (*1*). A more effective drug or drug combination, administered as a single dose, is clearly needed.

The findings presented here indicate that mefloquine may satisfy the need for a more effective, yet simple, treatment of drug-resistant infections of *P. falciparum*. To confirm the potential value of this drug as an antimalarial agent, further studies are indicated in areas of South America and Southeast Asia where drug resistance is a problem.

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6. Participants were healthy male inmate volunteers between 21 and 40 years of age. Procedures were explained in detail to each individual prior to obtaining his agreement to participate. The voluntary nature of participation and the right to withdraw at any time were emphasized. These studies, conducted at the Laboratory for Tropical Diseases at the Stateville Correctional Center, Joliet, Illinois, were approved by the Human Investigation Committee at Rush University, Chicago, Illinois.
7. Special emphasis was placed on evaluation for dizziness or related complaints by serial neurological examinations, cold pressor tests, caloric stimulation, and optokinetic nystagmus testing, audiograms, and electroencephalograms.
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12. Nonimmune individuals had no previous exposure to malaria and were treated with mefloquine during their initial attack of malaria. Partially immune individuals had previously been exposed to malaria, and acute clinical episodes had been suppressed with subcurative doses of other antimalarials. They were frequently asymptomatic at the time of treatment with mefloquine.
13. For patients infected with the Chesson strain of *P. vivax*, a daily dose of 30 mg of primaquine base was given for 14 days together with 1500 mg of chloroquine base administered over a period of 3 days.
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Alcoholic Hepatomegaly: Accumulation of Protein in the Liver

Abstract. *The hepatomegaly that appears after long-term feeding of ethanol results in accumulation of protein that is quantitatively as important as the increase in lipid. The bulk of protein accumulates in the soluble fraction of the cell. Hepatic albumin and transferrin concentrations increase and colchicine-binding protein decreases, thus suggesting an intrahepatic retention of export proteins.*

Hepatomegaly is a common manifestation of alcoholic liver disease. It is generally attributed to fat accumulation. However, there is no evidence that fat by itself can account for the increase in liver mass. Therefore, we undertook to determine whether there are cell constituents other than fat which contribute to ethanol-induced hepatomegaly. It was discovered that the feeding of ethanol results in deposition of export proteins in the cytosol.

Male rat littermates were pair-fed liquid diets as described (*1*) for 4 to 8 weeks. The diets contained 18 percent of calories as protein, 35 percent as fat, 11 percent as carbohydrate and 36 percent as either ethanol or additional carbohydrate. Ninety minutes after an intragastric administration of the respective diets (6 ml per 100 g of body weight), the rats weighing 180 to 360 g were killed under ether anesthesia by exsanguination from the aorta. The livers were excised and their weights (wet and dry), volume, total lipid, protein, and DNA contents were measured (*2*).

Livers from rats that were fed ethanol increased 30 percent both in volume and in wet weight (4.28 ± 0.13 g per 100 g of body weight compared to 3.34 ± 0.06 in controls; means ± S.E.M. of 24 pairs; $P < .001$ by the paired Student's *t*-test). The specific gravity of the liver was unchanged (1.009 ± 0.010 g/cm^3 compared to 1.016 ± 0.017 in controls) despite the doubling of hepatic lipids in the rats that were fed ethanol (Fig. 1). The increase in liver fat (151 ± 29 mg per 100 g of body weight) accounted for only half of the increase in liver dry weight (304 ± 40 mg per 100 g of body weight). In addition to the increase in liver lipid, there was a concomitant increase in liver protein (Fig. 1). The increase in protein (132 ± 41 mg per 100 g of body weight) accounted for almost all of the other half of the increased hepatic dry weight. Hepatic protein concentration did not change. This similarity in protein concentration indicates that water also increased in proportion to the increase in protein. Liver wet weight/dry weight ratios were similar in both groups of animals.

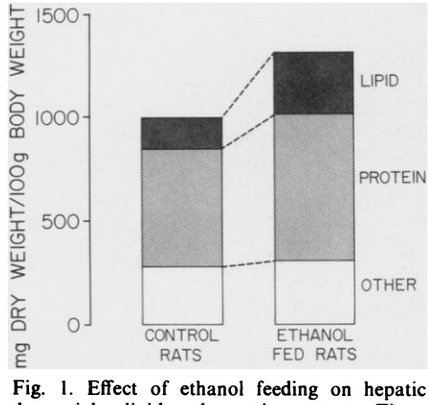

Fig. 1. Effect of ethanol feeding on hepatic dry weight; lipid and protein contents. These three differences are significant ($P < .01$).

In contrast to the increase in protein, DNA content of the liver remained unchanged (10.8 ± 0.5 mg per 100 g of body weight compared to 10.3 ± 0.4 in controls). This dissociation suggested that hepatomegaly was due to an increase in cell size rather than to an increase in cell number. This was verified in histologic sections of the liver. Hepatocytes occupied a significantly larger area (602 ± 43 μm^2 per cell) in livers from rats that were fed ethanol than in those from pair-fed controls (442 ± 36; 8 pairs; $P < .01$), even in zones where there was little visible fat. The 36 percent increase in size of the hepatocytes of rats that were fed ethanol can account for the hepatomegaly, since these cells contribute 87 percent of the liver volume (*3*). The number of mesenchymal cells per area increased by 17 percent in the livers of ethanol-fed rats ($P < .01$). However, because of the small size of the mesenchymal cells, their increased number does not contribute significantly to the hepatomegaly. The increase in hepatocyte size (observed in the