

Prophylaxis of *Plasmodium falciparum* Infection in a Human Challenge Model with WR 238605, a New 8-Aminoquinoline Antimalarial

RALF P. BRUECKNER,^{1*} TRINKA COSTER,² DAVID L. WESCHE,^{1,†}
MOSHE SHMUKLARSKY,³ AND BRIAN G. SCHUSTER¹

Division of Experimental Therapeutics¹ and Division of Communicable Diseases and Immunology,³ Walter Reed Army Institute of Research, Washington, D.C. 20307-5100, and Clinical Studies Branch, U.S. Army Medical Research Institute of Infectious Disease, Ft. Detrick, Frederick, Maryland 21702-5011²

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The prophylactic efficacy of WR 238605, a primaquine analog, was studied with a human *Plasmodium falciparum* challenge model. A single oral dose of 600 mg, administered 1 day prior to challenge, successfully protected three of four subjects. The fourth subject developed mild, oligosymptomatic malaria on day 31, with drug concentrations one-half of those in the protected individuals. WR 238605 appears to be a promising prophylactic drug for *P. falciparum* malaria.

Although mefloquine and doxycycline are currently highly effective for malarial prophylaxis (10), the side effects of these drugs, combined with emerging drug resistance, have resulted in the search for new prophylactic agents. One approach to new prophylactic drugs is the use of primaquine, previously used only to clear liver hypnozoites for prophylaxis against both *Plasmodium falciparum* and *Plasmodium vivax* malaria (5). WR 238605 succinate {(±)-8-[(4-amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline succinate} is a primaquine analog (Fig. 1) developed by the Walter Reed Army Institute of Research. In preclinical studies, WR 238605 demonstrated greater activity than primaquine against blood- and liver-stage parasites in vitro (7, 8). It has longer half-lives than primaquine in rodents (60 h), dogs (170 h), and monkeys (52 h) (2, 4). This combination of greater potency in vitro and longer half-life may be responsible for the higher efficacy of WR 238605 in vivo (9). In addition, WR 238605 demonstrated less toxicity than primaquine in animal models (2, 6). A previous safety study with humans demonstrated this drug to be well tolerated, with mild, transient gastrointestinal side effects (3). The half-life of WR 238605 in humans is a more favorable 14 days, rather than the short 4 to 6 h for primaquine or 16 h for doxycycline, and comparable to the 2- to 3-week half-life of mefloquine. We report the first clinical evidence of efficacy of WR 238605 for malaria prophylaxis in nonimmune human volunteers.

This was a randomized, placebo-controlled, double-blind study of healthy male and female volunteers. The protocol was approved by our institution's Human Use Committee and the Office of the Surgeon General of the United States Army and filed with the U.S. Food and Drug Administration. Written informed consent was obtained from each subject. Volunteers were excluded if there was any history of previous malaria infection or allergy to antimalarial drugs. WR 238605 (100-mg capsules) were obtained from the Walter Reed Army Institute

of Research drug inventory. Four subjects received a single, oral dose of 600 mg (base) of WR 238605, and two subjects received a matching placebo. Each dose was administered on an empty stomach 1 day prior to challenge. We used a human challenge model (1) in which volunteers were exposed to mosquitoes infected with a chloroquine-sensitive clone (NF54) of *P. falciparum*. Mosquitoes were then dissected to determine the salivary gland infectivity grade. Each volunteer was bitten by five infected mosquitoes with a salivary gland sporozoite grade of 2 or more (counted on a log scale of 0 to 4).

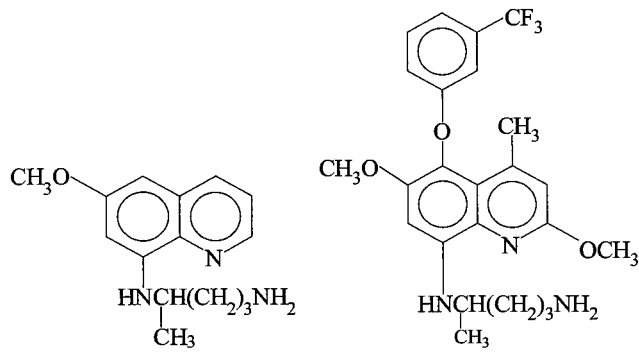
All six participants underwent blood examination for parasites daily for 3 weeks, beginning 5 days after sporozoite inoculation. Intermittent blood smears then continued for 45 to 65 days after inoculation. At least 100 high-power fields were examined. A slide was judged to be negative if no parasites were seen. Volunteers who developed parasitemia were treated with the standard oral regimen of 600 mg (base) of chloroquine followed by 300 mg at 6, 24, and 48 h (Aralen phosphate tablets; Sanofi-Winthrop Pharmaceuticals). Blood was also obtained for determination of WR 238605 concentrations by a previously validated high-performance liquid chromatography method (3). Volunteers were questioned periodically for symptoms.

The median age ± standard deviation of subjects was 25 ± 5 years, and their median weight was 75 ± 10 kg. WR 238605 was well tolerated, with only mild, transient side effects (headache and diarrhea) reported. Both subjects randomized to receive a placebo developed symptomatic parasitemia on day 10. Three of the drug-treated subjects remained aparasitemic, and one of the drug recipients (recipient 4) developed oligosymptomatic parasitemia on day 31 (Table 1). This individual had patency delayed by 3 weeks compared to that of subjects who received the placebo and had drug levels one-half of those seen in the protected subjects, although the small numbers in this study do not permit meaningful statistical analysis. Both the number and the severity of symptoms in subject 4 were dramatically reduced compared to symptoms of the two volunteers who received the placebo. The mean mosquito salivary gland infectivity grades and drug elimination half-lives were similar in all subjects.

This clinical study is the first to report the prophylactic efficacy of WR 238605 against *P. falciparum* malaria. Admin-

* Corresponding author. Mailing address: Department of Pharmacology, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100. Phone: (301) 295-7802 or (301) 295-7784. Fax: (301) 295-7755. E-mail: LTC_Ralf_Brueckner@WRSMTP-ccMail.Army.Mil.

† Present address: Ann Arbor, MI 48105.



Primaquine

WR 238605

FIG. 1. Structures of WR 238605 and primaquine.

istered as a single 600-mg oral dose, WR 238605 successfully prevented *P. falciparum* malaria in three of four nonimmune volunteers in this challenge model. Given the long elimination half-life of this drug, it is not possible to state whether the drug

TABLE 1. Results of study^a

Subject	Group	Mean mosquito salivary gland infectivity grade	Initial parasitemia (parasites/ μ l) (day)	C_{\max} (ng/ml)	$t_{1/2}$ (days)
1	Drug	3.8		453	17.2
2	Placebo	3.6	20 (10)		
3	Drug	3.8		417	15.2
4	Drug	3.4	27 (31)	244	14.4
5	Drug	3.2		489	13.3
6	Placebo	3.8	88 (10)		

^a Mosquito infectivity grades were counted on a log scale. C_{\max} , peak drug concentration in blood; $t_{1/2}$, elimination half-life.

exerts its effect as a true causal prophylactic, a blood schizonticide, or both. The promising, though preliminary, results from this first efficacy study and the long half-life suggest that WR 238605 is an excellent candidate drug for weekly prophylaxis against *P. falciparum* malaria. Studies are under way to determine the prophylactic efficacy of this drug against naturally acquired *P. falciparum* in larger populations.

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