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Antimalarial Activities of the 4-Quinolinemethanols WR-184,806 and WR-226,253†

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WR-184,806 and WR-226,253, two 4-quinolinemethanols structurally similar to WR-142,490 (mefloquine), have been studied in depth in owl monkeys infected with various drug-resistant and drug-susceptible strains of *Plasmodium falciparum* and *P. vivax* in an effort to provide support and guidance for projected evaluations in human volunteers. The results of these studies, confirmatory of preliminary appraisals, showed that WR-184,806 was approximately one-third as active as WR-142,490 against infections with a multidrug-resistant strain of *P. falciparum,* whereas WR-226,253 was twice as active. Additionally, the current studies showed: (i) that both WR-184,806 and WR-226,253 were significantly more active against infections with blood schizonts of *P. vivax* than against those of *P. falciparum;* (ii) that their activities against established infections with either *Plasmodium* species were functions of the total doses delivered, single doses being as effective as three or seven fractional doses given on successive days; (iii) that WR-184,806 could be administered intravenously as the phosphate salt and was curative via this route in single doses; and (iv) that based on comparative curative doses, WR-184,806 was slightly more active and WR-226,253 was seven times more active against infections with a multidrug-resistant strain of *P. falciparum* than was chloroquine against infections with a 4-aminoquinoline-susceptible strain.

As reported recently (16), pilot evaluations of the activities of 12 specially selected 4-quinolinemethanols in owl monkeys infected with various drug-susceptible and drug-resistant strains of *Plasmodium falciparum* identified five derivatives that were as active as or more active than chloroquine against infections with strains susceptible to this 4-aminoquinoline and equally effective against infections with strains resistant to chloroquine, quinine, and pyrimethamine. WR-142,490 (see structure, Fig. 1), the second member of this compound class to be examined in the human plasmodium-owl monkey model and overall the next most active representative of the group, was selected as a candidate for evaluation in human volunteers. This selection led to additional investigations of the activity of this agent in owl monkeys infected with blood schizonts of various strains of *P. falciparum* and *P. vivax* and in rhesus monkeys infected with sporozoites of *P. cynomolgi.* The results of these studies, presented elsewhere (16), together with those of preclinical toxicological and pharmacological investigations undertaken or monitored by the Department of Pharmacology, Walter Reed Army Institute of Research, provided information on efficacy and safety needed to initiate controlled evaluations in human volunteers. The therapeutic components of this investigation showed that: (i) single, well-tolerated doses of WR-142,490 (then named mefloquine) would cure established infections with either drug-susceptible or multidrug-resistant strains of *P. falciparum* (17); (ii) such doses would protect volunteers for at least 2 weeks against challenge with sporozoites of a multidrug-resistant strain of this plasmodium (11); and (iii) comparatively small doses would suppress infections with sporozoites of *P. vivax,* but even maximum tolerated doses would not cure such infections (3, 17). These appraisals of the suppressive, curative, and prophylactic activities of WR-142,490, supported by the results of limited field trials (6; E. Pearlman, E. Doberstyn, S. Sudsok, W. Theimanum, R. Kennedy, and C. Canfield, presentation at the 26th Annu. Meet. Am. Soc. Trop. Med. Hyg., November 1977, Denver, Colo.), stimulated plans for relatively large-scale field studies to be conducted under the auspices of the World Health Organization. These are currently underway (18).

Although the observations on WR-142,490

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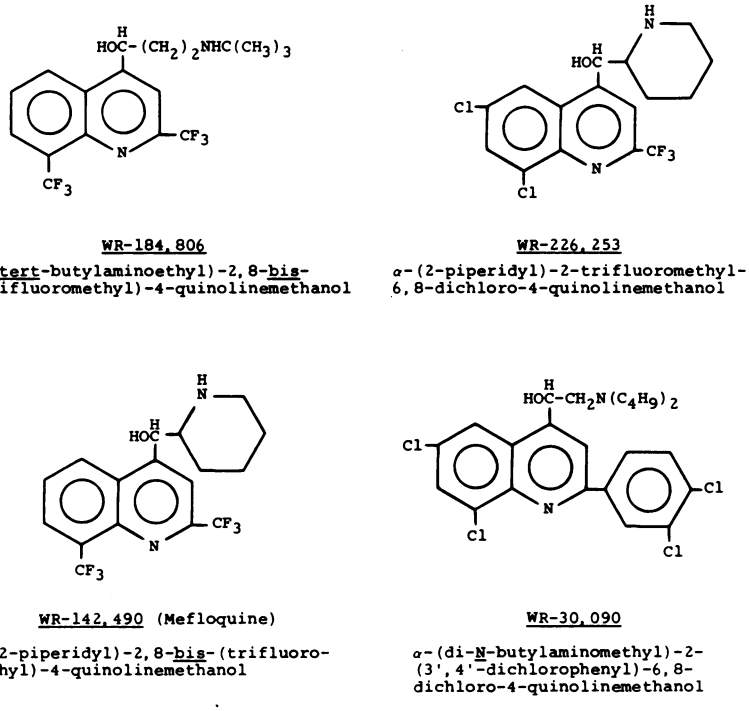

FIG. 1. *Comparison of structures of WR-184,806 and WR-226,253 with those of WR-142,490 (mefloquine) and WR-30,090.*

summarized above suggested that this compound might fill the current need for a broadly useful blood schizonticidal drug, those responsible for the new drug development phase of the current Malaria Research Program (sponsored by the U.S. Army Medical Research and Development Command) believed that other 4-quinolinemethanols with outstanding activity merited consideration for study in human volunteers. WR-184,806 and WR-226,253 (see structures, Fig. 1) were specifically identified as worthy of such attention. WR-184,806 (1), approximately one-third as active as WR-142,490 against infections with multidrug-resistant strains of *P. falciparum* in the owl monkey but more active than chloroquine against infections with 4-aminoquinoline-resistant strains (16), was the most effective of the quinolinemethanols with an alkylaminoalkyl substituent on the 4-carbinol. Since the nuclear configuration of WR-184,806 was the same as that of WR-142,490, it presented the opportunity of identifying the advantages or liabilities of the respective side chains. WR-226,253 (10), the most active of the quinolinemethanols evaluated in the human plasmodium-owl monkey model (16), approximately twice as active as WR-142,490, combined the structural features of the side chain and pyridine ring of the latter compound with the features of the benzene ring of WR-30,090 (see structure, Fig. 1). This structural similarity to the latter compound was of special interest. WR-30,090, prepared late in the World War II Malaria Chemotherapy Program (8), was the first quinolinemethanol evaluated in the human plasmodium-owl monkey model and in human volunteers in the current Malaria Research Program. Even though it exhibited no more than 1/20 of the activity of WR-142,490 in the above model (16), WR-30,090, administered at maximum tolerated daily doses for 6 days, almost invariably cured infections with multidrug-resistant strains of *P. falciparum* in human volunteers (4, 9) and in patients who had acquired the disease in the field (2, 7).

The decision to consider WR-184,806 and WR-226,253 for study in human volunteers led to expanded appraisals of the activities of these agents in owl monkeys infected with various strains of *P. falciparum* and *P. vivax*, with particular attention to the influence of the dosage regimen on efficacy. The results of these investigations are set forth in this report.

MATERIALS AND METHODS

Monkeys. Altogether, 191 adult or subadult owl monkeys (*Aotus trivirgatus griseimembra*) of northern Colombian origin were used in the investigations

summarized in this report. The group included essentially equal numbers of males and females, ranging from 800 to 1,120 g in weight at the time of assignment to experiments. Of the total, 159, used in evaluating the activities of WR-184,806, were imported directly from Barranquilla. The remaining 32, used exclusively for evaluating the activities of WR-226,253, were acquired from the Boston Biomedical Research Institute via an exchange arrangement with J. Denlinger and E. Balasz. This subgroup, previously used in studies of the visual apparatus, had been acquired from the Tarpon Zoo, Tarpon Springs, Fla. The procedures used in importing the above monkeys, adapting them to a caged environment and a laboratory diet, maintaining them in a healthy state, and handling them during the conditioning and drug evaluation periods were identical to those described in previous reports (12, 13).

Of the 191 monkeys, 110 with no previous malaria history were used in studies on infections with *P. falciparum*, 100 for direct evaluation of the activities of WR-184,806 and WR-226,253 and 10 as untreated or standard drug-treated controls. The remaining 81, all previously infected with *P. falciparum*, were used in studies on *P. vivax* infections, 75 for assessments of the activities of the two quinolinemethanols and 6 for control purposes. The original infections in all 81 had been treated early in the primary attack with either a quinazoline-sulfonamide combination or an α-amino-substituted *o*-cresol and cured. When assigned to the current study, each subject was more than 90 days removed from the last parasitic experience. As shown elsewhere (13), owl monkeys recovered from previous infections with various strains of *P. falciparum* are as susceptible as virgin subjects to challenge with blood schizonts of *P. vivax*.

Strains of plasmodia. The chloroquine-quinine-resistant Vietnam Oak Knoll and the chloroquine-quinine-pyrimethamine-resistant Vietnam Smith strains of *P. falciparum* and the pyrimethamine-resistant Vietnam Palo Alto strain of *P. vivax* were used in the current studies. The patient origins of these strains, the procedures used in adapting them to growth in owl monkeys with intact spleens and maintaining them at maximal virulence, the courses of untreated infections, and the dimensions of the susceptibility or resistance of standardized infections to treatment with chloroquine, quinine, and pyrimethamine have been described in earlier reports (13, 14).

Activity assessments. Since there was a substantial difference in the dimensions of the studies on WR-184,806 and WR-226,253, the scope of the evaluations of these agents will be considered separately. There were three phases to the assessment of the therapeutic activities of WR-184,806. The first was aimed at determining whether the phosphate salt of this compound, prepared for use in human volunteers, had the same activity against infections with the Vietnam Oak Knoll and Vietnam Smith strains of *P. falciparum* as the hydrochloride salt used in the pilot appraisals. The selection of the phosphate salt for the clinical studies rested on the demonstration that its water solubility in terms of base equivalent was approximately 24 times that of WR-184,806 monohydrochloride (T. Higuchi, INTER$_x$ Research Corp., Lawrence, Kans., personal communication). This comparative study, results of which will not be detailed here, showed that these salts were equally effective (in terms of base equivalents) in curing infections with the above strains when administered in a 7-day oral treatment regimen. This demonstration led to the second phase of the evaluation, aimed at determining the influence of various oral treatment schedules on the activity of WR-184,806 phosphate against infections with the Vietnam Oak Knoll and Vietnam Smith strains of *P. falciparum* and the Vietnam Palo Alto strain of *P. vivax*. The third phase of the assessment was concerned with the capacity of WR-184,806 to cure infections with the above strains when delivered intravenously in single doses or in three consecutive daily doses. This study was supported by the results of a preliminary appraisal of the tolerability of WR-184,806 when injected slowly over a 2-min period, an evaluation pursued in discarded owl monkeys previously cured of infections with both *P. falciparum* and *P. vivax*.

Compared with the above studies, the assessments of the activity of WR-226,253 were extremely limited, involving no more than a preliminary evaluation of the influence of various oral dosage regimens on the capacity of this compound to cure infections with the Vietnam Smith strain of *P. falciparum* and the Vietnam Palo Alto strain of *P. vivax*. Unfortunately, circumstances made it impossible to pursue an investigation of more appropriate dimensions. WR-226,253 was submitted for evaluation early in January 1976, approximately 4 months before conclusion of this malaria project. At that time, owl monkeys were in extremely short supply because of the embargo on exportation of wildlife imposed by the government of Colombia. As a result, the entire evaluation had to be carried out with 32 subjects acquired via the exchange arrangement with the Boston Biomedical Research Institute referred to previously.

All infections related to activity assessments were induced with an intravenous inoculum of 5×10^6 blood schizonts of the appropriate plasmodial strain. The preparation and delivery of this standard inoculum have been described elsewhere (14, 15). The procedures used in evaluating the activities of WR-184,806 and WR-226,253 were identical to those used in the broad assessments of the activities of chloroquine, quinine, and pyrimethamine (14), in pilot studies (15), and in the detailed appraisal of the therapeutic properties of WR-142,490 (16). Reports of these studies should be referred to for descriptions of procedures used to monitor parasitic events from the day after inoculation to cure, adjust dosage for retreatment in event of primary treatment failure or recrudescence, classify therapeutic responses, and calculate doses required for cure of 90% of infections (CD_{90}) and also for descriptions of how the basic test procedures provide information pertaining to parasite clearance rate and emergence of parasites resistant to the test compound.

Test agents and their administration. The preparations of WR-184,806 phosphate and WR-226,253 hydrochloride used in these studies were synthesized by Starks Associates, Inc., Buffalo, N.Y. Doses were always calculated as base equivalents and are so expressed throughout this report.

Solutions of the test compounds for delivery via

either the oral or the intravenous route were prepared fresh daily and were administered within 60 min of preparation. The procedures for preparing solutions for oral use and administering them via stomach tube were identical to those described in earlier reports (12, 14, 15). Intravenous administration of WR-184,806 was accomplished as follows. An amount of this compound, 5% in excess of that required for all monkeys to be treated, was placed in a sterile glass mortar (tube type) and, with the aid of light grinding with a Teflon pestle, was dissolved in the volume of iced sterile saline required for a concentration of 10.0 or 20.0 mg of base per ml. Solutions of such concentrations covered the requirements of the largest recipients of doses of 20.0 or 30.0 mg/kg; twofold-step subdilutions in sterile saline were used for delivery of smaller doses. From 1.5 to 2.0 ml of the appropriate concentration was injected slowly and steadily into the midsaphenous vein over a 2-min period.

RESULTS

The results of assessments of the activities of WR-184,806 administered orally to monkeys infected with the respective test strains are summarized in Table 1. The calculated CD_{90}'s, presented in column 10 of this table, show that single doses of WR-184,806 were as effective against infections with any one of these strains as the same amounts administered in three or seven fractions on consecutive days. The same data also show that the total doses required for regular cure of infections with the chloroquine-quinine-pyrimethamine-resistant Vietnam Smith strain of *P. falciparum* (60.0 to 80.0 mg/kg of body weight) were significantly larger than doses required for cure of infections with the chloroquine-quinine-resistant Vietnam Oak Knoll strain (25.0 to 27.0 mg/kg). The CD_{90} doses for infections with the pyrimethamine-resistant Vietnam Palo Alto strain of *P. vivax* (14.0 to 18.0 mg/kg) were probably significantly less than those for the Oak Knoll strain.

The results of assessments of the activities of WR-226,253 administered orally to monkeys infected with the Vietnam Smith strain of *P. falciparum* and the Vietnam Palo Alto strain of *P. vivax* are summarized in Table 2. Despite the limited dimensions of these appraisals, the data set forth in column 11 show clearly that the effectiveness of this compound, like that of WR-184,806, was a function of the total dose delivered, a single dose being as effective as the same amount administered in three or seven fractions on consecutive days. Comparison of the data in column 10 of Table 1 and column 11 of Table 2 indicates that WR-226,253, with CD_{90}'s of 8.0 to 12.0 mg/kg in the respective regimens, was from 5 to 10 times as active as WR-184,806 against infections with the Smith strain of *P. falciparum*. The difference in activity of the two agents against infections with the more susceptible Palo Alto strain of *P. vivax* was substantially less than that against the Smith strain, ranging from 2.5- to 3.5-fold.

Before turning to the activity of WR-184,806 administered intravenously, attention should be directed to the results of the preliminary tolerability study. This investigation showed that WR-184,806 administered as the phosphate salt was fully tolerated in single doses of 10.0, 20.0, or 30.0 mg of base per kg of body weight or in three consecutive daily doses of 10.0 or 20.0 mg/kg. Single doses of 40.0 and 60.0 mg/kg were, respectively, lethal to two of four and two of two recipients. Three consecutive daily doses of 30.0 mg/kg were lethal to two of four recipients. Fatal reactions to these doses were associated with severe clonic convulsions, persisting for 2 to 4 h before death and not controllable by administration of pentobarbital.

The calculated CD_{90}'s for WR-184,806 administered intravenously to monkeys infected with the Vietnam Oak Knoll strain of *P. falciparum* or the Vietnam Palo Alto strain of *P. vivax* were essentially the same for single-dose and three-daily-dose regimens, 22.0 and 25.0 mg/kg of body weight for infections with the former strain and 12.0 and 14.0 mg/kg for infections with the latter (Table 3, column 10). The similarity of these CD_{90}'s to those attained with the same oral treatment schedules (see Table 1) is an indirect indication that absorption of WR-184,806 from the gastrointestinal tract of the owl monkey is essentially complete. The approximate CD_{90}'s for WR-184,806 against infections with the Vietnam Smith strain are clearly larger than those for the Vietnam Oak Knoll strain, 45.0 mg/kg compared to 25.0 mg/kg in the three-dose regimen. It is worth noting that the calculated CD_{90} for single-dose treatment of infections with the Smith strain, also larger than that for the Oak Knoll strain, is in excess of the approximate 50% lethal dose level.

Two incidental observations made during the course of the various assessments merit attention. The first pertains to the times required for clearance of parasitemia in recipients of WR-184,806 and WR-226,253 and the influence of the dosage regimen thereon. The data summarized in columns 8 of Tables 1 and 3 and column 9 of Table 2 show that "days from delivery of first dose to parasite clearance" were essentially the same in recipients of curative doses of the above agents and were not influenced significantly by the dosage regimen. The second observation pertains to the impacts of initial therapeutic failure on the curative activities of WR-184,806 and WR-226,253. The data in columns 7 of Tables 1 and 3 and column 8 of Table 2 indicate that

TABLE 1. *Activities of WR-184,806, administered orally in various dosage schedules, against infections with the Vietnam Oak Knoll and Vietnam Smith strains of P. falciparum and the Vietnam Palo Alto strain of P. vivax*

Infection with:	Dosage regimen			Responses to treatment (no.)[a]			Mean day (range) from:		Approximate CD_{90} (total), mg/kg
	Individual dose (mg/kg)	No. of doses[b]	Total dose (mg/kg)	Effect on parasitemia: Suppressed	Effect on parasitemia: Clearance with recrudescence	Cured	Initial dose to parasite clearance[c]	Last dose to recrudescence	
P. falciparum, Vietnam Oak Knoll strain	17.5	1	17.5	—[d]	1 (R)	2 (P)	7.7(5–13)	19	25.0
	35.0	1	35.0	—	—	2 (P)	5	—	
	70.0	1	70.0	—	—	2 (P)	5	—	
	6.0	3	18.0	—	1 (R)	2 (P)	6.0(4–10)	18	25.0
	12.0	3	36.0	—	—	2 (P)	4	—	
	24.0	3	72.0	—	—	2 (P)	4	—	
	1.25	7	8.75	—	1 (P)	1 (P)	5.5(5–6)	12	27.0
	2.5	7	17.5	1 (P)	4 (P_2, R_2)	5 (P_3, R_2)	6.3(5–8)	14.0(10–22)	
	5.0	7	35.0	—	—	5 (P_2, R_3)	5.8(3–12)	—	
	10.0	7	70.0	—	—	3 (P_2, R)	7.3(6–9)	—	
P. falciparum, Vietnam Smith strain	17.5	1	17.5	2 (P)	2 (R)	—	4.5(4–5)	17	ca 85.0
	35.0	1	35.0	—	5 (P_2, R_3)	2 (R)	4.4(3–6)	22.0(10–36)	
	70.0	1	70.0	—	1 (R)	4 (P_2, R_2)	4.4(2–6)	32	
	6.0	3	18.0	1 (P)	5 (P)	1 (R)	5.0(4–6)	18.2(11–32)	60.0
	12.0	3	36.0	—	3 (P_2, R)	2 (R)	6.3(6–7)	18.7(16–20)	
	24.0	3	72.0	—	—	4 (R)	5.5(5–6)	—	
	2.5	7	17.5	9 (P_7, R_2)	1 (P)	—	8	7	70.0
	5.0	7	35.0	—	5 (P_2, R_3)	15 (P_2, R_{13})	6.2(4–9)	14.4(8–23)	
	10.0	7	70.0	—	1 (P)	8 (P_4, R_4)	7.3(6–10)	14	
P. vivax, Vietnam Palo Alto strain	4.37	1	4.37	—	2 (P)	—	4.5(3–6)	10.5(9–12)	14.0
	8.75	1	8.75	—	6 (P_3, R_3)	4 (P_2, R_2)	3.6(3–5)	17.0(13–21)	
	17.5	1	17.5	—	—	9 (P_5, R_4)	3.4(2–6)	—	
	35.0	1	35.0	—	—	3 (P)	3.3(2–5)	—	
	1.5	3	4.5	1 (P)	1 (P)	—	4	10	18.0
	3.0	3	9.0	—	6 (P, R_5)	5 (P_4, R)	4.2(3–6)	18.2(5–32)	
	6.0	3	18.0	—	1 (R)	6 (P_5, R)	4.0(3–6)	10	
	12.0	3	36.0	—	—	4 (P_3, R)	3.5(2–6)	—	

0.625	7	4.37	2 (P)	—	—	—	—	
1.25	7	8.75	1 (R)	7 (P_5, R_2)	5 (R)	5.9(4–9)	13.6(9–22)	
2.5	7	17.5	—	1 (R)	14 (P_5, R_9)	5.5(3–11)	26	17.0
5.0	7	35.0	—	—	8 (P_2, R_6)	4.1(3–6)	—	

[a] Letters in parentheses refer to treatment status of monkey. P, Initial treatment; R, retreatment. Subscripts indicate numbers of subjects in each category.
[b] Repetitive doses administered once daily on successive days.
[c] Days from first dose of drug to first of a series of five negative thick blood films on consecutive days. A single number without range implies identical clearance times for all subjects.
[d] —, Implies no subject in the respective category.

recurring infections were invariably eradicated by doses of these compounds that regularly cured previously untreated infections. This suggests that parasites resistant to these agents had not emerged during the unsuccessful treatment of the primary attack.

DISCUSSION

As indicated in the introduction to this report, pilot appraisals in owl monkeys infected with various strains of *P. falciparum* showed that WR-184,806 and WR-226,253 applied in 7-day oral treatment regimens effected cure of established infections with strains fully resistant to treatment with maximally tolerated doses of chloroquine, quinine, and pyrimethamine and that these quinolinemethanols were, respectively, roughly one-third and twice as active as WR-142,490 (16). From both qualitative and quantitative viewpoints, the results of the investigations summarized in this report are in agreement with these pilot assessments. The current studies go significantly further, however, in identifying the characteristics of WR-184,806 and WR-226,253. Specifically, they have shown that: (i) both compounds are highly active against infections with blood schizonts of *P. vivax* (a pyrimethamine-resistant strain); (ii) the activities of these agents against infections with either *P. falciparum* or *P. vivax* are a function of the total dose delivered rather than of the duration of treatment, a single dose being as effective as the same total amount administered in three or seven equal fractions on as many consecutive days; and (iii) WR-184,806 can be administered safely via the intravenous route and when so administered is curative in single doses. The latter quality of WR-226,253 was not examined for want of test animals and a water-soluble salt, restrictions which hopefully will be lifted. Although not detailed here, a very preliminary study (L. H. Schmidt, personal observation) showed that a single oral dose of WR-226,253, 17.5 mg/kg of body weight, would protect monkeys for at least 2 weeks from challenge with blood schizonts of the Vietnam Palo Alto strain of *P. vivax*.

The above findings indicate that both WR-184,806 and WR-226,253, like WR-142,490 studied in depth previously, are endowed with the activity characteristics of broadly useful blood schizonticidal drugs. The observations present no contraindication to plans for evaluating the antimalarial properties of these compounds in human volunteers. It is recognized, however, that the assessments of WR-226,253 have a very limited data base; hopefully, this will be ex-

TABLE 2. *Preliminary assessments of the activities of WR-226,253 against infections with the Vietnam Smith strain of P. falciparum and the Vietnam Palo Alto strain of P. vivax*

Infection with:	Dosage regimen			Responses to treatment (no.)[a]				Mean day (range) from:		Approximate CD_{90} (total), mg/kg
	Individual dose (mg/kg)	No. of doses[b]	Total dose (mg/kg)	Effect on parasitemia			Cured	Initial dose to parasite clearance[c]	Last dose to recrudescence	
				None	Suppressed	Clearance with recrudescence				
P. falciparum, Vietnam Smith strain	4.38	1	4.38	1 (P)	—[d]	—	—	—	—	
	8.75	1	8.75	—	—	—	3 (P_2, R)	7.0(6–8)	—	8.0
	17.5	1	17.5	—	—	—	1 (P)	6	—	
	1.46	3	4.38	1 (P)	—	—	—	—	—	
	2.92	3	8.76	—	—	1 (P)	2 (P, R)	7.3(7–8)	31	12.0
	5.84	3	17.5	—	—	—	2 (P, R)	6.0(5–7)	—	
	0.625	7	4.38	1 (P)	—	—	—	—	—	
	1.25	7	8.75	—	1 (P)	—	2 (P, R)	8.0(7–9)	—	12.0
	2.5	7	17.5	—	—	—	2 (P, R)	6	—	
P. vivax, Vietnam Palo Alto strain	1.1	1	1.1	1 (P)	—	—	—	—	—	
	2.2	1	2.2	—	2 (P, R)	—	—	—	—	
	4.38	1	4.38	—	—	1 (P)	2 (R)	4.3(4–5)	25	6.5
	8.75	1	8.75	—	—	—	2 (P, R)	4	—	
	0.365	3	1.1	—	1 (P)	—	—	—	—	
	0.73	3	2.2	—	—	1 (R)[e]	1 (P)	5.5(5–6)	—	
	1.46	3	4.38	—	—	1 (P)	3 (R)	4.3(4–5)	23	5.5
	2.92	3	8.75	—	—	—	3 (P_2, R)	3.3(3–4)	—	
	0.156	7	1.1	—	1 (P)	—	—	—	—	
	0.312	7	2.2	—	2 (P, R)	—	—	—	—	
	0.625	7	4.38	—	—	2 (R)	1 (P)	7.3(6–9)	24.0(19–29)	7.0
	1.25	7	8.75	—	—	—	3 (P_2, R)	5.3(4–6)	—	
	2.5	7	17.5	—	—	—	2 (P, R)	3.5(3–4)	—	

[a] Letters in parentheses refer to treatment status of monkey. P, Initial treatment; R, retreatment. Subscripts indicate numbers of subjects in each category.

[b] Repetitive doses administered once daily on successive days.

[c] Days from first dose of drug to first of a series of five negative thick blood films on consecutive days. A single number without range implies identical clearance times for all subjects.

[d] —, Implies no subject in the respective category.

[e] Death from cage trauma before completion of follow-up period.

TABLE 3. *Activities of WR-184, 806, administered intravenously in various dosage schedules, against infections with the Vietnam Oak Knoll and Vietnam Smith strains of P. falciparum and the Vietnam Palo Alto strain of P. vivax*

Infections with:	Dosage regimen			Responses to treatment (no.)[a]			Mean day (range) from:		Approximate CD_{90} (total), mg/kg
	Individual dose (mg/kg)	No. of doses[b]	Total dose (mg/kg)	Effect on parasitemia: Suppressed	Effect on parasitemia: Clearance with recrudescence	Cured	Initial dose to parasite clearance[c]	Last dose to recrudescence	
P. falciparum, Vietnam Oak Knoll strain	2.5	1	2.5	2 (P)	—[d]	—	—	—	
	5.0	1	5.0	4 (P_2, R_2)	—	—	—	—	
	10.0	1	10.0	3 (R)	2 (P, R)	1 (P)	4.7(4–5)	19.0(16–22)	22.0
	20.0	1	20.0	1 (R)	—	6 (P_2, R_4)	6.0(3–12)	—	
	0.83	3	2.5	2 (P)	—	—	—	—	
	1.67	3	5.0	4 (P_2, R_2)	—	—	—	—	
	3.33	3	10.0	2 (R)	2 (P)	—	7	16.5(11–22)	25.0
	6.67	3	20.0	—	3 (R)	5 (P_2, R_3)	5.5(3–8)	25.7(19–36)	
	10.0	3	30.0	—	—	3 (R)	5.3(5–6)	—	
P. falciparum, Vietnam Smith Strain	5.0	1	5.0	2 (P)	—	—	—	—	
	10.0	1	10.0	4 (P_2, R_2)	—	—	—	—	
	20.0	1	20.0	1 (P)	4 (P, R_3)	—	5.5(4–7)	14.3(12–21)	ca. 50.0
	30.0	1	30.0	—	5 (P, R_4)	2 (P, R)	4.4(4–5)	22.6(16–30)	
	1.67	3	5.0	3 (P_2, R)	—	—	—	—	
	3.33	3	10.0	4 (P_2, R_2)	—	1 (R)	4	—	
	6.67	3	20.0	—	4 (P_2, R_2)	3 (R)	5.3(3–8)	15.0(11–20)	ca. 45.0
	10.0	3	30.0	—	2 (P, R)	7 (P, R_6)	5.0(3–8)	13.0(7–19)	
P. vivax, Vietnam Palo Alto strain	2.5	1	2.5	2 (P)	1(R)	—	3	10	
	5.0	1	5.0	—	3 (P_2, R)	1 (R)	4.3(3–5)	14.0(8–19)	
	10.0	1	10.0	—	1 (P)	6 (P, R_5)	3.4(3–4)	25	12.0
	20.0	1	20.0	—	1 (P)	3 (R)	4.0(3–5)	42	
	0.83	3	2.5	2 (P)	—	—	—	—	
	1.67	3	5.0	3 (R)	2 (P)	1 (R)	4.7(4–5)	11.5(10–13)	
	3.33	3	10.0	—	3 (P_2, R)	3 (R)	4.3(4–5)	15.0(13–18)	14.0
	6.67	3	20.0	—	—	6 (P_2, R_4)	4.0(3–5)	—	

[a] Letters in parentheses refer to treatment status of monkey. P, Initial treatment; R, retreatment. Subscripts indicate numbers of subjects in each category.

[b] Repetitive doses administered once daily on successive days.

[c] Days from first dose of drug to first of a series of five negative thick blood films on consecutive days. A single number without range implies identical clearance times for all subjects.

[d] —, Implies no subject in the respective category.

panded before clinical study of this compound is undertaken.

Since decisions relating to evaluations of new agents in humans are influenced strongly by results of preclinical toxicological and pharmacological investigations, it is pertinent to take brief note of information accumulated in these areas. The preclinical evaluation of WR-226,253 is still in the planning stage. Extensive studies of the toxicology and pharmacology of WR-184,806 have been undertaken in or under the direction of the Department of Pharmacology of the Walter Reed Army Institute of Research (M. H. Heiffer, personal communication). Tolerability studies (C. C. Lee, Midwest Research Institute, Kansas City, Mo., personal communication) have shown that the acute toxicity of this compound for mice, rats, and dogs and its subacute toxicity for the latter two animals are relatively low, significantly less than the corresponding toxicity of WR-142,490 for mice and rats. Single daily doses of 150.0 mg/kg for 28 days were fully tolerated by rats, and single daily doses of 40.0 mg/kg for the same time period were fully tolerated by dogs. WR-184,806 did not exhibit phototoxicity in mice (M. Grenan, personal communication). Studies on ^{14}C-labeled WR-184,806 showed that this compound was well absorbed from the gastrointestinal tract of mice (5), rats, and rhesus monkeys (C. B. Hiremath, Litton Bionetics, Inc., Kensington, Md., personal communication), broadly distributed in tissues including erythrocytes (5), and slowly excreted. It exhibited a half-life in mice of 20 h, and in rhesus monkeys it exhibited a half-life of 52 h. In mice, at least, the compound was extensively metabolized with slow elimination of both parent compound and metabolites, primarily in the feces (5). Elimination of the label moiety was even slower in rhesus monkeys (C. B. Hiremath, personal communication).

Supported by the observations summarized above, a carefully controlled study of the tolerability of WR-184,806 in human volunteers was undertaken by K. G. Barry and R. C. Reba at the Washington Hospital Center (personal communication). The results indicated that single doses up to and including 1,000.0 mg were fully tolerated. Doses of 1,200.0 mg (in four subjects) and 1,400.0 mg (in two subjects) evoked lightheadedness, difficulties in focusing, headache, and nausea. These reactions were mild in intensity and less than 24 h in duration. A follow-up study, with a smaller group of volunteers, dealt with the tolerability of divided doses administered at 8-h intervals for 3 days. In this regimen, a total dose of 2,700.0 mg was well tolerated; a total dose of 3,600.0 mg provoked transient lightheadedness on the last treatment day. Comparison of these observations on WR-184,806 with those on WR-142,490 suggests that the tolerated doses of these compounds in humans are likely to be of similar magnitude. This suggestion in no way invalidates the appraisals in experimental animals, since the reactions evoked in volunteers are of the subjective type not identifiable in mice, rats, and dogs.

Before concluding this report, attention should be addressed to the question of whether the decision to pursue evaluations of the activities of WR-184,806 and WR-226,253 in volunteers is well founded inasmuch as WR-142,490 (mefloquine) exhibits such remarkable promise as a broadly useful blood schizonticidal drug. It appears to us that such studies are worth undertaking. The three derivatives of concern exhibit relatively similar antimalarial activities in the human plasmodium-owl monkey model and, if past experience is an indicator, will have similar activities in humans. The diverse chemical structures of these compounds could give them different pharmacological properties which would influence scheduling of doses, ease of administration, and patient acceptability. These are aspects of potential therapeutic utility that can only be evaluated in humans.

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