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DRUG EVALUATION IN THE PLASMODIUM FALCIPARUM-AOTUS MODEL

ANNUAL AND FINAL REPORT

Richard N. Rossan

(For the period 1 July 1976 to 15 July 1984)

September 1984

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Gorgas Memorial Laboratory
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Plasmodium vivax	chloroquine	amodiaquin
Aotus trivirgatus	pyrimethamine	primaquine

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Three strains of Plasmodium falciparum, Uganda Palo Alto, Vietnam Smith, and Vietnam Oak Knoll, and one strain (New Guinea Chesson) of P. vivax were adapted to Panamanian Aotus Trivirgatus. These models were used to evaluate the blood schizonticidal and curative activity of experimental antimalarial drugs. WR 228258, a 4-aminoquinoline, cured infections of P. falciparum as follows: a chloroquine-resistant strain by a dose of 2.0 mg base per kg (x 3 days), and a chloroquine-sensitive strain by a dose of 1.0 mg base per kg (x 3 days). →

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19. 4-aminoquinoline
8-aminoquinoline
quinazoline
quinolinemethanol
quinoline
triazine
acridine
acridinone
acridinol
indolquinoline
naphthalene-methanol
pteradineamine
pyrrolidone
thiosemicarbazone
desferrioxamine

20. Two 8-aminoquinolines, WR 225448 at a dose of 4.0 mg bse per kg (x 3 days) and WR 242511, at a dose of 1.0 mg base per kg (x 3 days), cured blood-induced P. vivax infections. An acridine, WR 243251, cured infections of a chloroquine-sensitive strain of P. falciparum at a dose of 1.0 mg base per kg (x 3 days) and infections of a chloroquine-resistant strain at a dose of 4.0 mg base per kg (x 3 days). Blood induced infections of P. falciparum or P. vivax were cured by WR 250547 (acridinol) by a dose of 1.0 mg base per kg (x 3 days).

SUMMARY

The aim of the work summarized herein was to establish Plasmodium falciparum and P. vivax blood-induced infections in Panamanian Aotus trivirgatus and to employ these models for the evaluation of experimental antimalarial drugs. Three strains of P. falciparum, Uganda Palo Alto, Vietnam Smith, and Vietnam Oak Knoll, and the Chesson strain of P. vivax, previously adapted (in another laboratory) to Aotus of Colombian origin, were obtained and adapted to Panamanian Aotus.

Comparison of infection parameters of the three falciparum strains in Panamanian and Colombian Aotus indicated that the virulence of these strains, as indicated by lower mortality rates, was less in Panamanian than in Colombian monkeys. Maximum parasitemias in the primary attack of infections with the Vietnam Smith and Vietnam Oak Knoll strains were similar in both models, but lower for infections with the Uganda Palo Alto strain in Panamanian monkeys.

Although there were quantitative differences from the course of infections in the Colombian Aotus, in which the infections were first characterized, the Panamanian Aotus were a satisfactory model for the evaluation of experimental antimalarial drugs.

Evaluation of the antimalarial activity of chloroquine, pyrimethamine, quinine and mefloquine against P. falciparum infections indicated that:

1. The three strains, Uganda Palo Alto, Vietnam Smith, and Vietnam Oak Knoll retained their respective drug sensitivity or resistance in Panamanian Aotus.

2. This model could be used to evaluate the blood schizonticidal and curative activity of potential antimalarial agents.

Chloroquine and pyrimethamine, administered for three consecutive days, cleared parasitemias and cured infections, of the New Guinea Chesson strain of P. vivax in Panamanian Aotus at total mg per kg doses comparable to those administered for seven consecutive days to Colombian Aotus.

Six amodiaquin analogues were evaluated for their capacity to cure infections of chloroquine-sensitive and chloroquine-resistant strains of P. falciparum. These 4-aminoquinolines cured infections of chloroquine-resistant strains at comparable doses as required for cure of chloroquine-sensitive strains, and were 25 to 50 times more active than amodiaquin. WR 228258 cured infections of the Uganda Palo Alto strain (chloroquine-sensitive) at a total dose of 3.0 mg base per kg, whether administered as a single dose or 1.0 mg base per kg (x 3 days). Infections of the chloroquine-resistant Vietnam Smith strain were cured by WR 228258 at a total dose of 6.0 mg base per kg, administered either as a single dose or 2.0 mg base per kg (x 3 days).

Primaquine and six 8-aminoquinolines were evaluated against blood-induced infections of P. vivax and P. falciparum.

Primaquine did not cure primary infections of P. vivax at a dose of 52.8 mg base per kg (x 3 days).

WR 225448, at a dose of 4.0 mg per kg (x 3 days), and WR 242511, at a dose of 1.0 mg base per kg (x 3 days), cured blood-induced P. vivax infections. Blood-induced P. falciparum infections were cured by WR 225448, but at doses 4 to 8 times greater than required for P. vivax infections.

Six quinazoline drugs were evaluated against P. falciparum infections and WR 158122 was re-assessed by administering for three consecutive days. WR 158122 was as effective against infections of the pyrimethamine-sensitive Vietnam Oak Knoll strain as it was when administered for seven consecutive days. Cross resistance to infections of the Vietnam Smith strain was confirmed. Two quinazolines, WR 232716 and WR 150015, at doses of 0.25 and 1.25 mg base per kg (x 3 days), respectively, cured Vietnam Oak Knoll infections. No quinazoline in this group had blood schizonticidal/curative activity against Vietnam Smith infections at doses without concomitant drug toxicity.

Neither of the two quinolinemethanols tested, WR 226663 and WR 215440, were as effective against infections of the Vietnam Smith strain as WR 142490 (mefloquine).

WR 169626AA, an acetylated triazine, and administered as the hydrochloride salt, had little antimalarial activity against infections of the Vietnam Smith strain. The curative activity of the free base, WR 169626AB, was less than that of the hydrochloride salt.

WR 169627AA was re-assessed in a 3-day regimen. WR 169627 was more active than WR 169626 against infections of the pyrimethamine-resistant Vietnam Smith strain; WR 169626 was more active than WR 169627 against infections of the pyrimethamine-sensitive Vietnam Oak Knoll strain.

Six new acridines and floxacrine (WR 233602) were evaluated against P. falciparum infections. One acridine, WR 243251, had greater antimalarial activity than floxacrine. Infections of the Uganda Palo Alto strain were cured by a dose of 1.0 mg base per kg (x 3 days), and a dose of 4.0 mg base per kg (x 3 days) cured Vietnam Smith infections.

Of the two acridinols evaluated against P. falciparum and P. vivax infections, WR 250547 was the most active. Primary infections of the Vietnam Smith strain of P. falciparum and of the Chesson strain of P. vivax were cured by a dose of 1.0 mg base per kg (x 3 days).

Eight drugs of diverse chemical classes were evaluated against P. falciparum infections. Seven of these drugs had little or no blood schizonticidal activity. When WR 079520, desferrioxamine, was administered via osmotic pumps implanted subcutaneously, parasitemias were suppressed in 7 of 9 Aotus. Desferrioxamine administered via pump plus twice daily injection cleared the parasitemia in one monkey, and significantly suppressed the parasitemia in one Aotus.

During the course of these studies, five drugs were shown to be active

against plasmodial infections in Aotus:

1. WR 228258, a 4-aminoquinoline, cured at comparable doses infections of chloroquine-resistant and chloroquine-sensitive strains of P. falciparum,

2. Two 8-aminoquinolines, WR 225448 and WR 242511, cured blood-induced infections of P. vivax. In contrast, primaquine was not active against the trophozoite stages of P. vivax.

3. WR 24351, (an acridine), cured, at comparable doses, infections of chloroquine-sensitive and chloroquine-resistant strains of P. falciparum.

4. An acridinol, WR 250547, at a dose of 1.0 mg base per kg (x 3 days) cured infections of P. falciparum or P. vivax.

FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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INTRODUCTION

Aotus trivirgatus, of Colombia origin, previously had been used for the pre-clinical evaluation of experimental antimalarial drugs (Schmidt 1973, 1978a, 1978b, 1978c). The aim of the studies summarized in the present report was to establish a human malaria model in Panamanian Aotus for this purpose.

Drug evaluations were accomplished from July 1976 through June 1984, and the results summarized in the appropriate sections, grouped by the chemical class of experimental drugs evaluated. Detailed results have presented in the Annual Reports for each contract.

EXPERIMENTAL PROCEDURES

The monkeys employed for drug evaluation studies were feral Aotus trivirgatus, captured on the Isthmus of Panama. After 3 - 6 month adaptation period to laboratory conditions, the animals were incorporated into experimental studies.

Three strains of Plasmodium falciparum and one strain of P. vivax, previously adapted to and passaged in Aotus of Colombian origin (Schmidt 1978a), were adapted to Panamanian Aotus as follows:

P. falciparum

Uganda Palo Alto - sensitive to chloroquine and quinine, RIII resistant pyrimethamine.

Vietnam Smith - RIII resistant to chloroquine, pyrimethamine and quinine.

Vietnam Oak Knoll - RIII resistant to chloroquine and quinine, sensitive to pyrimethamine.

P. vivax

Chesson - sensitive to chloroquine, pyrimethamine and quinine.

Infected blood from a donor monkey was diluted with chilled saline (0.85%) such that each milliliter contained the required number of parasites; either 5×10^4 or 5×10^6. Aotus were inoculated intravenously with the former number for maintenance of passage lines, while the latter amount was inoculated to initiate drug evaluation studies.

Blood was collected from marginal ear capillaries for blood films which were stained with Giemsa. Evaluation of parasitemia was: negative - if no parasites were seen after examining a thick blood film for at least five minutes; <10 parasites per cmm - if parasites could be demonstrated only on a thick blood film; the number of parasites per cmm, as enumerated by the Earle - Perez method (1931). Blood films were prepared daily, beginning on the day after inoculation and continued until no parasites could be detected on thick blood films for at least three or more consecutive days. Thereafter, films were made twice weekly and if they remained negative for 100 days, the infections were considered cured.

The schema depicted in Figure 1 represents the design of a typical drug evaluation study. Drug administration was usually initiated on day 5 after inoculation of 5×10^6 parasites, when the parasitemia approximated 5×10^3 per cmm. Stock solutions of water soluble drugs were prepared with a distilled water and stored at 8°c for the treatment period. If a drug was water insoluble, a suspension of the requisite amount of drug was prepared daily in 0.3% methylcellulose (in distilled water). Drug dosages were calculated as milligrams base per kilogram of body weight. Except where noted, drugs were administered orally by gastric intubation with a No. 14 French urethral catheter.

Standard antimalarial drugs were administered for seven consecutive days, whereas experimental drugs were administered either once or daily for three consecutive days.

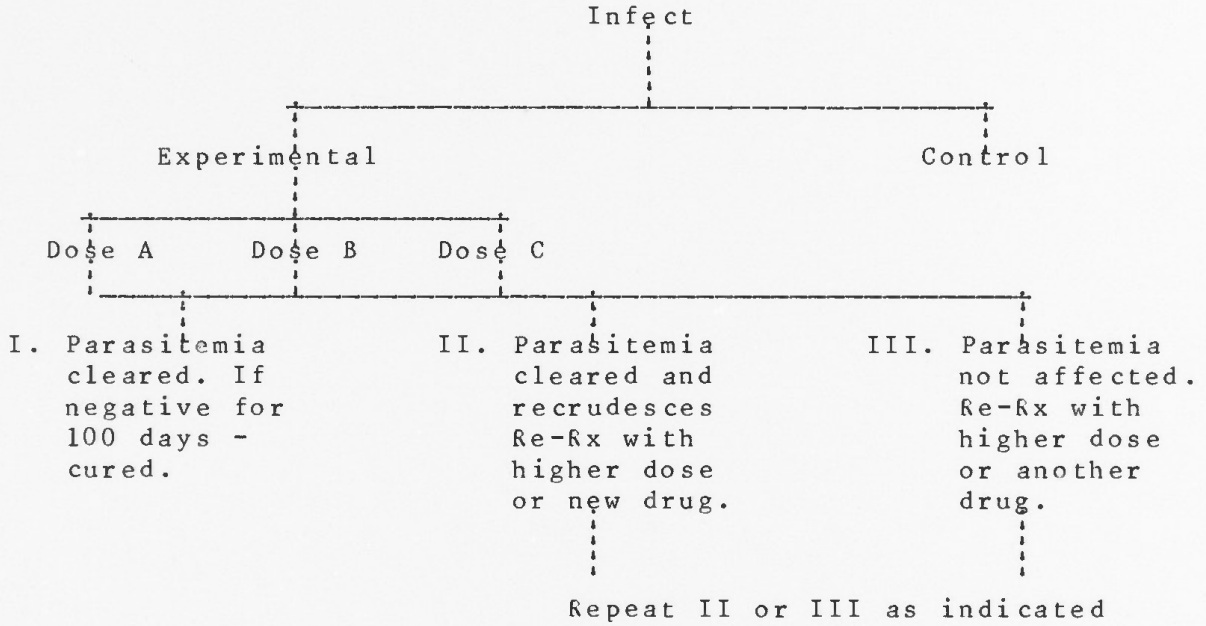
Aotus, cured of P. falciparum infection were fully susceptible to blood-induced infection with P. vivax (Schmidt, 1978a). Select drugs were evaluated in the P. vivax - Aotus model.

FIGURE 1

SCHEMA FOR DRUG EVALUATION AGAINST

PLASMODIUM FALCIPARUM AND P. VIVAX TROPHOZOITE

INDUCED INFECTIONS IN AOTUS TRIVIRGATUS



COMPARISON OF THE COURSE OF UNTREATED PLASMODIUM FALCIPARUM INFECTIONS IN PANAMANIAN AND COLOMBIAN AOTUS MONKEYS

Since the first experimental laboratory model for experimental drug evaluation used Aotus of Colombian origin (Schmidt 1973, 1978 a, b. c), a comparison between the course of untreated infections in Panamanian and Colombian Aotus was important:

1. To quantify the similarity or dissimilarity between the two models, and

2. To demostrate that Panamanian Aotus could serve in lieu of the Colombian Aotus for drug evaluation studies.

A manuscript (Rossan, et al) has been submitted for publication detailing and comparing the course of infection in the two models. Parameters of blood-induced infections of the Uganda Palo Alto, Vietnam Smith, and Vietnam Oak Knoll strains of P. falciparum in 395 Panamanian Aotus were compared with Schmidt's report (1978a) of infections in 665 Aotus of Colombian origin. The passage levels of the three strains differed in the two monkey models, in that parasites were passaged in Colombian Aotus from 1968 to 1975, and in Panamanian Aotus from 1976 to 1984.

The virulence of these strains in Panamanian owl monkeys was less than in Colombian monkeys, as shown by lower mortality rates in Panamanian Aotus, although the evolution of parasitemias was more rapid than in the Colombian Aotus model. Peak parasitemias in the primary attack of infections with the Vietnam Oak Knoll and Vietnam Smith strain were similar in both models, but lower for infections with the Uganda Palo Alto strain in Panamanian monkeys.

In Panamanian Aotus with self-limited infections, the primary patent period was shorter than in Colombian owl monkeys, while the time from the end of the primary attack to the first recrudescence was longer in Panamanian monkeys than in Colombian.

Panamanian owl monkeys were good experimental hosts for blood-induced infections of three strains of P. falciparum. Although there were minor quantitative differences from the course of infections in the Colombian owl monkey, in which the infections were first characterized, the Panamanian Aotus were an equally satisfactory model for the evaluation of experimental antimalarial drugs.

ACTIVITY OF CHLOROQUINE (WR 1544BM; BN: AR 20613), PYRIMETHAMINE (WR 2978AO; BN: AG 5046), QUININE (WR 2976AY; BN: AW 23860), AND MEFLOQUINE (WR 142490 AB; BN: BG 14436) AGAINST INFECTIONS OF THREE STRAINS OF PLASMODIUM FALCIPARUM

The spectrum of antimalarial susceptibility/resistance of infections with the Uganda Palo Alto, Vietnam Smith and Vietnam Oak Knoll strain of P. falciparum was defined in the Colombian Aotus by Schmidt (1973, 1978 b). Once these strains were established in Panamanian Aotus, it was essential to confirm, albeit in limited trials, if similar results were obtained in the new model. The results are summarized in Tables 1 and 2.

Uganda Palo Alto Strain:

The drugs, for assessment of activity against infections of this strain, were given for three consecutive days, with the dosage adjusted to deliver the equivalent total mg base per kg dose as was administered in 7 - day treatments by Schmidt (1973, 1978 b). Infections of this chloroquine - sensitive strain were cured with a total dose of 24.0 and 48.0 mg base per kg, respectively.

The response of this pyrimethamine - resistant strain was as anticipated, in that no cures, with one exception, were obtained at doses of 1.0, 2.0, or 4.0 mg base per kg (x 3 days).

Suppression of parasitemia, but not cure, was observed following quinine treatment. The total dose of 290 mg base per kg administered over 7 - days, that cured infections of this strain in Colombian Aotus could not be administered in a single tolerated daily dose in a three day regimen (93.0 mg per kg vs the maximum tolerated dose of 80.0 mg per kg).

Vietnam Smith Strain -

Schmidt (1978 b) reported that infections in Colombian Aotus with this P. falciparum strain were RIII resistant to daily maximum tolerated doses of chloroquine (20.0 mg base per kg), pyrimethamine (2.5 mg base per kg), and quinine (80.0 mg base per kg).

Drugs were administered for seven consecutive days. As indicated in Table 1, a dose of 20.0 mg base per kg (x 7 days) of chloroquine did not cure Vietnam Smith infections in Panamanian Aotus. Pyrimethamine, at a dose of 0.625 mg base per kg (x 7 days), cured an aberrant infection, but doses of 1.25 and 2.5 mg base per kg (x 7 days) did not cure primary infections. Retreated infections were cured with these doses.

A maximum tolerated dose of quinine of 80.0 mg base per kg (x 7 days)did not cure Vietnam Smith infections (Table 2).

Schmidt et al (1978 d) reported on the antimarial activity of WR 142490 (mefloquine). Doses of 2.5 and 5.0 mg base per kg (x 7 days) cured infections of the multi-resistant Vietnam Smith strain in Colombian Aotus and as shown in Table 2, also cured infections in Panamanian Aotus.

Vietnam Oak Knoll Strain -

Resistance to chloroquine was confirmed in the Panamanian Aotus model as a dose of 20.0 mg base per kg (x 7 days) did not clear or cure primary infections of this strain (Table 1). Sensitivity to pyrimethamine was confirmed as shown in Table 1. Doses of 1.25 and 2.5 mg base per kg (x 7 days) cured infections. A maximum tolerated dose of 80.0 mg base per kg (x 7 days) did not cure infections (Table 2).

Mefloquine cured infections of the Vietnam Oak Knoll strain at doses of 7.25, 2.5 and 5.0 mg base per kg (x 7 days). Similar activity was shown by Schmidt et al (1978d).

CONCLUSIONS

Although limited in scope, evaluation of the antimalarial activity of chloroquine, pyrimethamine, quinine, and mefloquine against P. falciparum infections indicated that:

1. The three strains, Uganda Palo Alto, Vietnam Smith, and Vietnam Oak Knoll retained their respective drug sensitivity/resistance in Panamanian Aotus and

2. This model could be used to evaluate the blood schizonticidal and curative activity of potential antimalarial agents.

TABLE 1

SUMMARY OF THE ACTIVITY OF CHLOROQUINE (WR 1544 BM; BN: AR 20613), AND PYRIMETHAMINE (WR 2978 AO; BN: AG 5046) AGAINST INFECTIONS OF THREE STRAINS OF PLASMODIUM FALCIPARUM

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
				CHLOROQUINE				
UPA	6.0	2.0	0/2	0/2			0/2	0/2
	24.0	8.0	2/2	1/2			2/2	1/2
	48.0	16.0	2/2	1/2			2/2	1/2
SM	8.75	1.25	0/2	0/2			0/2	0/2
	35.0	5.0	0/2	0/2			0/2	0/2
	140.0	20.0	0/2	0/2			0/2	0/2
OKN	8.75	1.25	0/2	0/2			0/2	0/2
	35.0	5.0	0/2	0/2			0/2	0/2
	140.0	20.0	0/2	0/2			0/2	0/2
				PYRIMETHAMINE				
UPA	3.0	1.0	1/2	1/2			1/2	1/2
	6.0	2.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2			0/2	0/2
SM	4.4	0.625	1/2	1/2	2/2	1/2	3/4	2/4
	8.75	1.25	0/2	0/2	2/2	1/2	2/4	1/4
	17.5	2.5	0/2	0/2	2/2	1/2	2/4	1/4
OKN	4.4	0.625	2/2	0/2			2/2	0/2
	8.75	1.25	2/2	2/2			2/2	2/2
	17.5	2.5	3/3	1/2			3/3	1/2

UPA= Uganda Palo Alto; SM= Vietnam Smith; OKN= Vietnam Oak Knoll

TABLE 2

SUMMARY OF THE ACTIVITY OF QUININE (WR 2976 AY; BN: AW 23860), AND MEFLOQUINE (WR 142490 AB: BN: BG 14436) AGAINST INFECTIONS OF THREE STRAINS OF PLASMODIUM FALCIPARUM

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
				QUININE				
UPA	48.0	16.0	0/2	0/2			0/2	0/2
	96.0	32.0	0/2	0/2			0/2	0/2
	192.0	64.0	1/2	0/2			1/2	0/2
SM	140.0	20.0	0/2	0/2			0/2	0/2
	280.0	40.0	0/2	0/2			0/2	0/2
	560.0	80.0	0/2	0/2			0/2	0/2
OKN	140.0	20.0	0/2	0/2			0/2	0/2
	280.0	40.0	0/2	0/2			0/2	0/2
	560.0	80.0	1/2	0/2			1/2	0/2
				MEFLOQUINE				
SM	4.4	0.625	1/1	0/1			1/1	0/1
	8.75	1.25	1/1	0/1	3/3	3/3	4/4	3/4
	17.5	2.5	2/2	2/2	2/2	2/2	4/4	4/4
	35.0	5.0	2/2	2/2	2/2	2/2	4/4	4/4
OKN	8.75	1.25	2/2	2/2			2/2	2/2
	17.5	2.5	3/3	2/3			3/3	2/3
	35.0	5.0	2/2	2/2			2/2	2/2

UPA= Uganda Palo Alto; SM= Vietnam Smith; OKN= Vietnam Oak Knoll

ACTIVITY OF CHLOROQUINE (WR 1544BM; BN: AR 20613) AND PYRIMETHAMINE (WR 2978AO; BN: BG 5046) AGAINST INFECTIONS OF THE NEW GUINEA CHESSON STRAIN OF PLASMODIUM VIVAX

Evaluation of the response of blood-induced infections with this strain in Colombian Aotus (Schmidt, 1978b) to standard antimalarial drugs indicated that chloroquine at a dose of 1.25 mg base per kg (x 7 days) suppressed parasitemias and that doses of either 2.5 or 5.0 mg base per kg (x 7 days) cured infections. Pyrimethamine at a dose of 1.25 mg base per kg (x 7 days) cured infections in 4 of 4 Colombian Aotus. This strain of P. vivax is considered sensitive to both chloroquine and pyrimethamine.

After adaptation of the Chesson vivax strain to Panamanian Aotus, the activity of chloroquine and pyrimethamine was evaluated at doses administered once daily for three consecutive days. The doses were adjusted to deliver the equivalent total mg base per kg of drug that was administered to Colombian monkeys over for seven days.

As shown in Table 3, the curative activity of chloroquine was confirmed as total doses of 17.4 and 35.1 mg base per kg. Pyrimethamine at a total dose of 8.7 mg base per kg cured all infections, primary and recrudescent.

CONCLUSIONS

The capacities of chloroquine and pyrimethamine, when administered for three consecutive days, to clear parasitemias and cure infections of the New Guinea Chesson strain of *P. vivax* in Panamanian *Aotus* were comparable to those determined for 7 - day treatments by Schmidt (1978b) in Colombian *Aotus*.

TABLE 3

SUMMARY OF THE ACTIVITY OF CHLOROQUINE (WR 1544 BM; BN: AR 20613) AND PYRIMETHAMINE (WR 2978 AO; BN: AG 5046) AGAINST INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
				CHLOROQUINE				
	8.7	2.9	2/3	0/3			2/3	0/3
	17.4	5.8	2/2	2/2	3/3	3/3	5/5	5/5
	35.1	11.7	3/3	3/3			3/3	3/3
				PYRIMETHAMINE				
	0.132	0.044	1/3	0/3			1/3	0/3
	0.525	0.175	3/3	2/3	3/3	3/3	6/6	5/6
	2.1	0.7	2/2	1/2	1/1	1/1	3/3	2/3
	8.7	2.9	3/3	3/3	1/1	1/1	4/4	4/4

EVALUATION OF THE ANTIMALARIAL ACTIVITIES OF SIX AMODIAQUIN ANALOGUES AND AMODIAQUIN AGAINST INFECTIONS OF CHLOROQUINE-SENSITIVE AND CHLOROQUINE-RESISTANT STRAINS OF PLASMODIUM FALCIPARUM

Following the demostration of P. falciparum resistance to chloroquine (Moore and Lanier 1961), further studies (Young 1961) indicated cross resistance of such strains to various 4-aminoquinolines, notably amodiaquin, when administered at therapeutic doses to infected individuals. Studies were initiated by Schmidt in 1969 to assess the activity of select 4-aminoquinolines against chloroquine resistant strains of P. falciparum in the Colombian night monkey model. Schmidt et al (1977) demostrated that amodiaquin, at doses well tolerated by Aotus, effected cure of infections resistant to the maximally tolerated dose of chloroquine. Based upon Schmidt's initial data, that cross resistance to the 4-aminoquinolines was not absolute, there was renewed during the mid-1970's in pursuing amodiaquin analogues as candidate antimalarials.

A total of six amodiaquin analogues was evaluated for their capacity to cure infections of chloroquine-sensitive and chloroquine-resistant strains of P. falciparum in Panamanian Aotus. One of these drugs, WR 228258, was submitted as an I. N. D.

A. Amodiaquin - WR 2977AB (BN: AG 92043)

For the purpose of comparison, it was important to ascertain if the reported observations of Schmidt et al (1977) could be duplicated in a 3-day regimen in the Panamanian Aotus model. He found that infections of the chloroquine-sensitive Uganda Palo Alto strain were cured with amodiaquin at a dose of 10.0 mg per kg (x 7 days), and infections of the chloroquine-resistant Vietnam Oak Knoll strain were cured with a dose of 20.0 mg per kg (x 7 days). Amodiaquin was not tested against Vietnam Smith infections, but amopyroquin cured such infections at a dose of 20.0 mg per kg (x 7 days).

The activity of amodiaquin, used as the dihydrochlorate dihydrate form, against P. falciparum injections in Panamanian Aotus is summarized in Table 4. A total dose of 70.0 mg base per kg of amodiaquin cured infections of the Uganda Palo Alto strain. Primary infections of the Oak Knoll strain were not cured with amodiaquin with a total dose of 140.0 mg base per kg, but 3 of 4 recrudescent infections were cured.

A total dose of 140.0 mg base per kg cured one primary and two recrudescent infections of the chloroquine-resistant Vietnam Smith strain.

A 3-day treatment with amodiaquin is in agreement with that for a 7-day treatment in that infections of chloroquine-resistant P. falciparum strain can be cured, but at high dosage levels.

B. WR 228258AC (BN: BH 38968)
WR 228258AG (BN: BJ 23346)

Pilot evaluation (Table 5) of WR 228258AC (free base) showed that doses of 1.0 mg base per kg (x 3 days) and higher cured infections of the chloroquine-

sensitive Uganda Palo Alto strain. Primary infections and recrudescences of the multi-resistant Vietnam Smith strain were cured with doses of 1.0, 2.0, and 4.0 mg base per kg (x 3 days). Limited evaluation against infections of the chloroquine-resistant Vietnam Oak Knoll showed similar activity as against the Vietnam Smith.

Additional studies with this 4-aminoquinoline used WR 228258AG, the dihydrochloride salt. Treatment for three consecutive days at doses of 1.0 or 2.0 mg base per kg cured Uganda Palo Alto infections (Table 6). When the total number of milligrams base of drug administered over a 3-day period was administered as a single dose, the activity was virtually identical (Table 7). Single doses of 3.0 or 6.0 mg base per kg cured primary infections and were as effective as 1.0 or 2.0 mg base per kg given for three days.

The dihydrochloride salt of WR 228258 was slightly less effective then the free base against infections of the chloroquine-resistant Vietnam Smith strain. Doses of 1.0, 2.0 and 4.0 mg base per kg (x 3 days) of the free base, which cured all infections, were not uniformly curative by the dihydrochloride salt (Table 6). The curative activity of the dihydrochloride salt against primary Vietnam Smith infections of a single dose and three doses, was similar only at total doses of 6.0 and 12.0 mg base kg (Table 7). No cures were obtained when 3.0 mg base per kg was administered as a single dose.

C. WR 225449AB (BN: BG 94925)

Pilot evaluation of this amodiaquin analogue showed high antimalarial activity (Table 8). A dose of 2.0 mg base per kg (x 3 days) cured 7 of 7 Uganda Palo Alto infections, 6 of 9 Vietnam Smith infections, and 2 of 2 Vietnam Oak Knoll infections. Doses of 4.0 and 8.0 mg base per kg (x 3 days) cured Vietnam Smith and Vietnam Oak Knoll infections.

D. WR 219774AB (BN: BH 35903)

As shown in Table 8, this drug at a dose of 2.0 mg base per kg (x 3 days) cured 3 of 3 primary and 3 of 3 recrudescent infections of the Uganda Palo Alto strain. Three of 5 infections of the Vietnam Smith strain were cured with a dose of 1.0 mg base per kg (x 3 days) and a dose of 2.0 mg base per kg (x 3 days) cured 4 of 4 primary and 4 of 4 recrudescent infections.

E. WR 247170AB (BN: BJ 86423)

Pilot evaluation (Table 9) indicated that Uganda Palo Alto and Vietnam Smith infections were cured at a dose of 1.0 mg base per kg (x 3 days).

F. WR 233637AB (BN: BH 49596)

Doses of 4.0 or 8.0 mg base per kg (x 3 days) cured primary infections of the Uganda Palo Alto strain (Table 9), and a dose of 16.0 mg base per kg (x 3 days) cured 2 of 2 primary infections of the Vietnam Smith strain.

G. WR 228979AB (BN: BH 08326)

This 4-aminoquinoline (Table 9) at a dose of 1.0 mg base per kg (x 3 days) cured 3 of 3 primary Uganda Palo Alto infections. One of one Vietnam Smith infection was cured at a dose of 4.0 mg base per kg (x 3 days), and infections of the Vietnam Oak Knoll strain were cured at doses of 2.0 mg base per kg (x 3 days) and higher.

CONCLUSIONS

The amodiaquin analogues tested against infections of chloroquine-sensitive and chloroquine-resistant strains of P. falciparum showed remarkable activity when compared with that of amodiaquin. Infections of chloroquine-resistant strains were cured at comparable curative dose levels for chloroquine-sensitive strains. The analogues were 25 to 50 times more active than amodiaquin.

If WR 228258 retains curative activity against chloroquine-resistant falciparum infections in man, an important addition will have been made to the antimalarial armamentarium.

TABLE 4

SUMMARY OF THE ACTIVITY OF WR 2977 AB (BN: AG 92043), AMODIAQUIN, AGAINST INFECTIONS OF THREE STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
UPA	17.4	5.8	2/2	1/2			2/2	1/2
	35.1	11.7	2/2	1/2			2/2	1/2
	69.9	23.3	2/2	2/2	1/2	1/2	3/3	3/3
SM	35.1	11.7	1/2	0/2			1/2	0/2
	69.9	23.3	2/2	0/2	2/2	0/2	2/4	0/4
	140.1	46.7*	2/2	1/2	5/5	2/5	7/7	3/7
OKN	35.1	11.7	1/2	0/2			1/2	0/2
	69.9	23.3	2/2	1/2	2/2	0/2	4/4	1/4
	140.1	46.7*	2/2	0/2	4/4	3/4	6/6	3/6

UPA= Uganda Palo Alto; SM= Vietnam Smith; OKN= Vietnam Oak Knoll

* Administered as two equal fractions at 8:00 A.M. and 5:00 P.M.

TABLE 5

SUMMARY OF THE ACTIVITY OF WR 228258 AC* (BN: BH 38968) AGAINST INFECTIONS OF THREE STRAINS OF PLASMODIUM FALCIPARUM

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
UGANDA PALO ALTO	0.375	0.125	0/1	0/1			0/1	0/1
	0.75	0.25	0/1	0/1	1/1	1/1	1/2	1/2
	1.5	0.5	1/1	0/1	1/1	1/1	2/2	1/2
	3.0	1.0	1/1	1/1	1/1	1/1	2/2	2/2
	6.0	2.0	4/4	4/4			4/4	4/4
	12.0	4.0	1/1	1/1			1/1	1/1
VIETNAM SMITH	0.375	0.125	0/1	0/1			0/1	0/1
	0.75	0.25	0/1	0/1	1/1	1/1	1/2	1/2
	1.5	0.5	4/4	0/4			4/4	0/4
	3.0	1.0	4/4	3/4	3/3	2/3	7/7	5/7
	6.0	2.0	1/1	1/1	5/5	5/5	6/6	6/6
	12.0	4.0	1/1	1/1			1/1	1/1
VIETNAM OAK KNOLL	0.375	0.125	0/1	0/1			0/1	0/1
	0.75	0.25	0/1	0/1			1/1	0/1
	1.5	0.5	1/1	0/1	1/1	1/1	2/2	1/2
	3.0	1.0	1/1	0/1	1/1	1/1	2/2	1/2
	6.0	2.0	1/1	1/1	1/1	1/1	2/2	2/2
	12.0	4.0	1/1	1/1			1/1	1/1

* Free base

TABLE 6

SUMMARY OF THE ACTIVITY OF WR 228258 AG* (BN: BJ 23346), ADMINISTERED FOR THREE CONSECUTIVE DAYS, AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
UGANDA PALO ALTO	0.75	0.25	0/4	0/4			0/4	0/4
	1.5	0.5	1/4	0/4	4/4	3/4	5/8	3/8
	3.0	1.0	4/4	4/4	5/5	5/5	9/9	9/9
	6.0	2.0	4/4	4/4			4/4	4/4
VIETNAM SMITH	1.5	0.5	2/4	0/4			2/4	0/4
	3.0	1.0	4/4	2/4	4/4	4/4	8/8	6/8
	6.0	2.0	4/4	1/4	2/2	2/2	6/6	3/6
	12.0	4.0	4/4	2/4	3/3	2/3	7/7	4/7
	24.0	8.0			2/3	2/3	2/3	2/3
	48.0	16.0			1/1	1/1	1/1	1/1

* Dihydrochloride salt

TABLE 7

SUMMARY OF THE ACTIVITY OF WR 228258 AG* (BN: BJ 23346), ADMINISTERED AS A SINGLE DOSE, AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
UGANDA	0.75	0.75	2/4	0/4			2/4	0/4
PALO ALTO	1.5	1.5	2/4	0/4			2/4	0/4
	3.0	3.0	4/4	4/4	4/4	3/4	8/8	7/8
	6.0	6.0	4/4	4/4	5/5	5/5	9/9	9/9
VIETNAM	1.5	1.5	2/4	0/4			2/4	0/4
SMITH	3.0	3.0	4/4	0/4			4/4	0/4
	6.0	6.0	4/4	2/4	4/4	4/4	8/8	6/8
	12.0	12.0	4/4	3/4	6/6	5/6	10/10	8/10
	24.0	24.0			2/2	2/2	2/2	2/2

* Dihydrochloride salt

TABLE 8

SUMMARY OF THE ACTIVITY OF TWO AMODIAQUIN ANALOGUES AGAINST INFECTIONS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS		
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED	
				WR 225449 AB (BN: BG 94925)					
UGANDA	1.5	0.5	1/4	0/4			1/4	0/4	
PALO ALTO	3.0	1.0	1/4	1/4	1/1	1/1	2/5	2/5	
	6.0	2.0	1/1	1/1	6/6	6/6	7/7	7/7	
VIETNAM	1.5	0.5	0/1	0/1			0/1	0/1	
SMITH	3.0	1.0	4/4	1/4	1/1	1/1	5/5	2/5	
	6.0	2.0	4/4	3/4	5/5	3/5	9/9	6/9	
	12.0	4.0	1/1	1/1	1/1	1/1	2/2	2/2	
	24.0	8.0	1/1	1/1			1/1	1/1	
	48.0	16.0	1/1	0/1			1/1	0/1	(Died Day 47 Post
OAK KNOLL	0.75	0.25	0/1	0/1			0/1	0/1	
	1.5	0.5	0/1	0/1			0/1	0/1	
	3.0	1.0	1/1	0/1	1/1	0/1	2/2	0/2	
	6.0	2.0	1/1	1/1	1/1	1/1	2/2	2/2	
	12.0	4.0	1/1	1/1			1/1	1/1	
	24.0	8.0	1/1	1/1			1/1	1/1	
				WR 219774 AB (BN: BH 35903)					
UGANDA	1.5	0.5	2/4	0/4			2/4	0/4	
PALO ALTO	3.0	1.0	2/4	2/4	4/4	3/4	6/8	5/8	
	6.0	2.0	3/3	3/3	3/3	3/3	6/6	6/6	
VIETNAM	0.0468	0.0156	0/1	0/1			0/1	0/1	
SMITH	0.1875	0.0625	0/1	0/1			0/1	0/1	
	0.27	0.09			0/1	0/1	0/1	0/1	
	0.6	0.2			0/1	0/1	0/1	0/1	
	0.75	0.25	0/1	0/1			0/1	0/1	
	1.5	0.5	0/4	0/4			0/4	0/4	
	3.0	1.0	5/5	3/5	5/6	4/6	10/11	7/11	
	4.2	1.4	1/1	0/1			1/1	0/1	
	6.0	2.0	4/4	4/4	4/4	4/4	8/8	8/8	
	12.0	4.0	1/1	1/1			1/1	1/1	
	48.0	16.0	1/1	1/1			1/1	1/1	

TABLE 9

SUMMARY OF THE ACTIVITY OF THREE AMODIAQUIN ANALOGUES AGAINST INFECTIONS OF PLASMODIUM FALCIPARUM

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
			WR 2471701 AB (BN: BJ 86423)					
UGANDA PALO ALTO	0.75	0.25	0/1	0/1			0/1	0/1
	1.5	0.5	1/2	1/2	2/2	1/1	3/4	2/3
	3.0	1.0	3/3	3/3	2/2	2/2	5/5	5/5
VIETNAM SMITH	0.75	0.25	0/2	0/2			0/2	0/2
	1.5	0.5	2/2	0/2	2/2	2/2	4/4	2/4
	3.0	1.0	2/2	2/2	5/5	5/5	7/7	7/7
	12.0	4.0			2/2	2/2	2/2	2/2
			WR 233637 AB (BN: BH 49596)					
UGANDA PALO ALTO	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	2/2	2/2	2/2	2/2	4/4	4/4
	24.0	8.0	2/2	2/2			2/2	2/2
VIETNAM SMITH	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	0/1	0/1	0/3	0/3
	24.0	8.0	0/2	0/2			0/2	0/2
	48.0	16.0	2/2	2/2			2/2	2/2
	96.0	32.0			3/4	1/4	3/4	1/4
	192.0	64.0			3/3	2/3	3/3	2/3
	384.0	128.0			1/1	1/1	1/1	1/1
			WR 228979 AB (BN: BH 08326)					
UGANDA PALO ALTO	1.5	0.5	3/4	0/4			3/4	0/4
	3.0	1.0	4/4	3/3	4/4	3/4	8/8	6/7
	6.0	2.0			1/1	1/1	1/1	1/1
VIETNAM SMITH	3.0	1.0	2/3	0/3			2/3	0/3
	6.0	2.0	4/4	2/4	5/5	4/5	9/9	6/9
	12.0	4.0	1/1	1/1			1/1	1/1
	24.0	8.0	1/1	0/1	1/1	1/1	2/2	1/2
	48.0	16.0	2/2	2/2			2/2	2/2
VIETNAM OAK KNOLL	0.75	0.25	0/1	0/1			0/1	0/1
	3.0	1.0	1/1	0/1			1/1	0/1
	6.0	2.0	1/1	1/1	2/2	2/2	3/3	3/3
	12.0	4.0	1/1	1/1			1/1	1/1
	24.0	8.0	1/1	1/1			1/1	1/1
	48.0	16.0	1/1	1/1			1/1	1/1

EVALUATION OF THE ANTIMALARIAL ACTIVITIES OF SIX 8-AMINOQUINOLINES AND PRIMAQUINE AGAINST BLOOD-INDUCED INFECTIONS OF PLASMODIUM VIVAX AND PLASMODIUM FALCIPARUM

Radical cure of sporozoite induced infections of P. vivax or P. ovale currently requires the administration of two drugs - a schozonticide to eliminate the parasites in the erythrocytes and another drug to eliminate the persisting hepatic stages. A single drug, acting against both the blood and tissue stages, would be ideal. Primaquine is presently the only drug active against the liver stages of malaria; but is toxic when administered to patients with glucose - 6 phosphate dehydrogenase deficiency.

Of 4000 compounds screened for causal prophylactic and radical curative activity (Davidson, et al 1981), WR 225448, 4-methyl -5- (3- trifluoromethyl-phenoxy) -6- methoxy-8- [(4-amino-1methylbutyl) amino] quinoline succinate was five times more active than primaquine in curing persisting exoerythrocytic infections of P. cynomolgi in rhesus monkeys. Moreover, trophozoite-induced infections of P. cynomolgi were cured by a dose of 1.0 mg per kg administered for seven days.

WR 225448 and five other primaquine analogues were evaluated for blood schizonticidal activity against infections of P. vivax and P. faiciparum in Aotus .

A. WR 2975AW (BN: BJ 82411), Primaquine

For comparative purposes, the activity of primaquine was assessed against the blood stages of the Chesson strain of P. vivax. While the diphosphate salt of primaquine was used, no correction was made when calculating drug dosages, as primaquine and WR 225448 were compared on an equimolar basis.

The data in Table 10 show that primary P. vivax infections were not cured by primaquine at a dose of 52.8 mg per kg (x 3 days). Retreated infections were cured but at high doses, viz 52.8 and 105.6 mg per kg (x 3 days).

B. WR 225448AG (BN: BH 58522)
WR 225448AF (BN: BH 35761)

Two lots of WR 225448, administered as the succinate salt and considered identical were used for antimalarial evaluation. When tested against blood-induced P. vivax infections, no salt correction was made (as indicated in the above section).

P. vivax:

As shown in Table 11, parasitemias were cleared at doses of 1.0 mg per kg (x 3 days) and greater, and cures were obtained at doses of 4.0 or 16.0 mg per kg (x 3 days).

P. falciparum:

Vietnam Oak Knoll strain -

Pilot evaluation (Table 12) of WR 225448 indicated no activity at doses of 0.25, 1.0, 2.0, or 4.0 mg base per kg (x 3 days) against primary parasitemias. Treatments with doses of 4.0 or 8.0 mg base per kg (x 3 days) cleared parasitemias but did not cure infections.

Uganda Palo Alto strain -

As shown in Table 13, WR 225448 at doses of 4.0 mg base per kg (x 3 days) and higher cleared primary parasitemias, but cured infections in 33% of the monkeys. Retreatments at doses of 2.0 mg base per kg (x 3 days) and higher consistently cleared parasitemias but did not cure 100% of the infections.

When the total number of milligrams administered for 3 days was given over a 7-day period, primary parasitemias were cleared consistently at a total dose of 24.0 mg base per kg (Table 13). Two of three primary infections and 1 of 3 primary infections were cured at a total dose of 48.0 and 96.0 mg base per kg, respectively. Retreatments with a total dose of 12.0 mg base per kg and higher uniformly cleared all parasitemias; all infections were cured at a total dose of 96.0 or 192.0 mg base per kg.

Vietnam Smith strain -

Primary parasitemias were cleared (Table 14) consistently with doses of 8.0, 16.0, or 32.0 mg base per kg (x 3 days), but only the latter dose cured infections (2 of 3). Retreatments with doses of 2.0 mg base per kg (x 3 days) consistently cleared parasitemias, but did not cure all infections, except at a dose of 128.0 mg base per kg (x 3 days).

Administration of WR 225448 for seven days (Table 14), cleared primary parasitemias at a total dose of 24.0 mg base per kg and higher. One of two primary infections was cured with 13.72 mg base per kg (x 7 days)- a total dose of 96.0 mg base per kg. Retreatments, for seven days, at total doses of 12.0 mg base per kg and higher cleared all parasitemias while 100% of the infections were cured only at total doses of 48.0 and 192.0 mg base per kg.

C. WR 242511AB (BN: BJ 78592)

Pilot evaluation of this 8-aminoquinoline against showed (Table 15) that infections of the Uganda Palo Alto strain of P. falciparum were consistently cured with a dose of 32.0 mg base per kg (x 3 days). One of three primary and 3 of 3 recrudescent infections of the Vietnam Smith strain were cured with a dose of 32.0 mg base per kg (x 3 days). A dose of 64.0 mg base per kg (x 3 days) cured 2 of 2 Vietnam Smith infections.

Blood induced infections of P. vivax were cured (Table 15) with doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days. Additional evaluation of WR 242511 against vivax infections is projected.

D. WR 238605AB (BN: BJ 83119)

Data in Table 16 indicate that primary and recrudescent infections of P. falciparum (Uganda Palo Alto strain) were consistently cured at a dose of 32.0 mg base per kg (x 3 days) of WR 238605. A dose of 16.0 mg base per kg (x 3 days) cured 11 of 12 Vietnam Smith infections, primary and recrudescent.

Primary parasitemias of P. vivax (Table 16) were cleared with doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days). One of 2 such infections was cured with a dose of 4.0 mg base per kg (x 3 days) and 2 of 2 primary infections were cured with a dose of 16.0 mg base per kg (x 3 days).

E. WR 249420AB (BN: BK 56537)

As shown in Table 17, this drug cured primary infections of the Uganda Palo Alto strain of P. falciparum at a dose of 4.0 mg base per kg (x 3 days) and primary infections of the Vietnam Smith strain at doses of 4.0 or 16.0 mg base per kg (x 3 days).

Primary parasitemias of P. vivax were cleared at doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days), and the latter dose cured infections in 2 of 2 Aotus.

F. WR 250505AA (BN: BK 50419)

At the doses used, this 8-aminoquinoline had no schizonticidal activity against infections of the Uganda Palo Alto strain of P. falciparum (Table 18).

Primary parasitemias of P. vivax (Chesson strain) were not cleared at doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days). Retreatments cured 2 of 11 infections.

G. WR 250531AA (BN: BK 50768)

As indicated in Table 19, retreatment of Uganda Palo infections of P. falciparum at a dose of 32.0 mg base per kg (x 3 days) cleared 2 of 3 parasitemias and cured the infection in 1 of 3 Aotus.

This 8-aminoquinoline did not cure blood-induced P. vivax infections at doses of 1.0, 4.0, 16.0, or 32.0 mg base per kg (x 3 days).

CONCLUSIONS

Two of the 8-aminoquinolines, at low doses, cured blood-induced P. vivax infections - WR 225448 at a dose of 4.0 mg base per kg (x 3 days) and WR 242511 at a dose of 1.0 mg base per kg (x 3 days). WR 225448 was 13 times more active than primaquine in curing blood-induced infections of the chesson strain of P. vivax. Blood induced infections of P. falciparum were cured by WR 225448, but at doses 4 to 8 times greater than required for P. vivax infections.

If WR 225448 or an analogue is active as both a tissue and blood schizonticide/curative in sporozoite-induced P. vivax infections in man, then a long-sought objective will be achieved, viz a single curative drug for naturally-acquired P. vivax infections.

TABLE 10

SUMMARY OF THE ACTIVITY OF WR 2975AW (BN: BJ 82411), PRIMAQUINE, AGAINST BLOOD-INDUCED INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
	2.48	0.825	2/3	1/3			2/3	1/3
	5.0	1.65	0/4	0/4			0/4	0/4
	9.9	3.3	0/4	0/4	1/6	0/6	1/10	0/10
	39.6	13.2	3/3	0/3	10/10	4/10	13/13	4/13
	79.2	26.4	3/3	0/3	8/8	6/8	11/11	6/11
	158.4	52.8	3/3	0/3	5/5	4/5	8/8	4/8
	316.8	105.6			4/4	4/4	4/4	4/4

TABLE II

SUMMARY OF THE ACTIVITY OF WR 225448AG (BN: BH 58522) AGAINST BLOOD-INDUCED INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
	3.0	1.0	3/3	0/3			3/3	0/3
	6.0	2.0	5/5	0/5	2/2	2/2	7/7	2/7
	12.0	4.0	4/4	4/4	4/4	4/4	8/8	8/8
	48.0	16.0	3/3	3/3			3/3	3/3

TABLE 12

SUMMARY OF THE ACTIVITY OF WR 225448AF (BN: BH 35761) AGAINST INFECTIONS OF THE VIETNAM OAK KNOLL STRAIN OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
	0.75	0.25	0/1	0/1			0/1	0/1
	3.0	1.0	0/1	0/1			0/1	0/1
	6.0	2.0			0/1	Died Day 1 Post Rx, malaria		
	12.0	4.0	0/1	0/1	1/1	0/1	1/2	0/2
	24.0	8.0			1/1	0/1	1/1	0/1

TABLE 13

SUMMARY OF THE ACTIVITY OF WR 225448 AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
			DRUG ADMINISTERED FOR THREE CONSECUTIVE DAYS					
	3.0	1.0	0/1	0/1			0/1	0/1
	6.0	2.0	0/5	0/5	1/1	0/1	1/6	0/6
	12.0	4.0	3/5	0/5	4/4	3/4	7/9	3/9
	24.0	8.0	3/3	0/3	7/7	5/7	10/10	5/10
	48.0	16.0	3/3	1/3	4/4	2/4	7/7	3/7
	75.0	25.0	1/1	1/1			1/1	1/1
	96.0	32.0	3/3	1/3	3/3	2/3	6/6	3/6
	192.0	64.0			2/2	1/2	2/2	1/2
	384.0	128.0			1/1	1/1	1/1	1/1
			DRUG ADMINISTERED FOR SEVEN CONSECUTIVE DAYS					
	3.0	0.43	0/1	0/1			0/1	0/1
	6.0	0.86	0/5	0/5			0/5	0/5
	12.0	1.71	2/5	1/5	5/5	3/5	7/10	4/10
	24.0	3.43	3/3	0/3	6/6	3/6	9/9	3/9
	48.0	6.86	3/3	2/3	3/3	2/3	6/6	4/6
	96.0	13.71	3/3	1/3	4/4	4/4	7/7	5/7
	192.0	27.4			2/2	2/2		

TABLE 14

SUMMARY OF THE ACTIVITY OF WR 225448 AGAINST INFECTIONS OF THE VIETNAM SMITH STRAIN OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
			DRUG ADMINISTERED FOR THREE CONSECUTIVE DAYS					
	0.75	0.25	0/1	0/1			0/1	0/1
	3.0	1.0	0/1	0/1			0/1	0/1
	6.0	2.0	0/4	0/4	1/1	0/1	1/5	0/5
	12.0	4.0	0/5	0/5	6/6	3/6	6/11	3/11
	24.0	8.0	3/3	0/3	7/7	2/7	10/10	2/10
	48.0	16.0	3/3	0/3	8/8	6/8	11/11	6/11
	96.0	32.0	3/3	2/3	4/4	3/4	7/7	5/7
	192.0	64.0			2/2	1/2	2/2	1/2
	384.0	128.0			1/1	1/1	1/1	1/1
			DRUG ADMINISTERED FOR SEVEN CONSECUTIVE DAYS					
	6.0	0.86	0/4	0/4			0/4	0/4
	12.0	1.71	0/3	0/3	3/3	2/3	3/6	2/6
	24.0	3.43	2/2	0/2	4/4	1/4	6/6	1/6
	48.0	6.86	2/2	0/2	2/2	2/2	2/4	2/4
	96.0	13.72	2/2	1/2	4/4	2/4	6/6	3/6
	192.0	27.4			3/3	3/3		

TABLE 15

SUMMARY OF THE ACTIVITY OF WR 242511AB (BN: BJ 78592) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM AND ONE STRAIN OF PLASMODIUM VIVAX

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
				PLASMODIUM FALCIPARUM				
UPA	3.0	1.0	0/2	0/2	1/1	1/1	1/3	1/3
	12.0	4.0	4/4	2/4	2/2	1/2	6/6	3/6
	48.0	16.0	4/4	3/4	3/3	3/3	7/7	6/7
	96.0	32.0	3/3	3/3	1/1	1/1	4/4	4/4
SMITH	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	2/2	0/2	2/2	1/2	3/4	1/4
	48.0	16.0	4/4	1/4	3/3	3/3	7/7	4/7
	96.0	32.0	3/3	1/3	3/3	3/3	6/6	4/6
	192.0	64.0			2/2	2/2	2/2	2/2
				PLASMODIUM VIVAX				
CHESSON	3.0	1.0	2/2	2/2			2/2	2/2
	12.0	4.0	2/2	2/2			2/2	2/2
	48.0	16.0	2/2	2/2			2/2	2/2

TABLE 16

SUMMARY OF THE ACTIVITY OF WR 238605AB (BN: BJ 83119) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM AND ONE STRAIN OF PLASMODIUM VIVAX

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
				PLASMODIUM FALCIPARUM				
UPA	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	4/4	0/4	2/2	0/2	6/6	0/6
	48.0	16.0	4/4	3/4	6/6	4/6	10/10	7/10
	96.0	32.0	2/2	2/2	2/2	2/2	4/4	4/4
	192.0	64.0			1/1	*	1/1	*
SMITH	3.0	1.0	0/4	0/4	2/2	1/2	2/6	1/6
	12.0	4.0	0/4	0/4	7/7	4/7	7/11	4/11
	48.0	16.0	3/3	3/3	9/9	8/9	12/12	11/12
	96.0	32.0			1/1	1/1	1/1	1/1
				PLASMODIUM VIVAX				
CHESSON	3.0	1.0	2/2	0/2			2/2	0/2
	12.0	4.0	2/2	1/2	2/2	2/2	4/4	3/4
	48.0	16.0	2/2	2/2	1/1	0/2	3/3	2/4
	96.0	32.0			1/1	1/1	1/1	1/1

* Died 60 days post-Rx, negative 58 days.

TABLE 17

SUMMARY OF THE ACTIVITY OF WR 249420AB (BN: BK 56537) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM AND ONE STRAIN OF PLASMODIUM VIVAX

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
				PLASMODIUM FALCIPARUM				
UPA	0.75	0.25	0/2	0/2			0/2	0/2
	3.0	1.0	0/2	0/2	3/5	3/5	3/7	3/7
	12.0	4.0	2/2	2/2	6/6	3/5	8/8	5/7
SMITH	3.0	1.0			3/3	1/3	3/3	1/3
	12.0	4.0	2/2	2/2	4/4	1/4	6/6	3/6
	48.0	16.0	2/2	2/2	6/6	3/6	8/8	5/8
	96.0	32.0			3/3	2/3	3/3	2/3
	192.0	64.0			1/1	1/1	1/1	1/1
				PLASMODIUM VIVAX				
CHESSON	3.0	1.0	2/2	1/2			2/2	1/2
	12.0	4.0	2/2	1/2*	1/1	1/2	3/3	2/3
	48.0	16.0	2/2	2/2			2/2	2/2

* 1 Died day 8 post-Rx, intercurrent infection

TABLE 18

SUMMARY OF THE ACTIVITY OF WR 250505AA (BN: BK 50419) AGAINST INFECTIONS OF ONE STRAIN OF PLASMODIUM FALCIPARUM AND ONE STRAIN OF PLASMODIUM VIVAX

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
				PLASMODIUM FALCIPARUM				
UPA	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	0/1	0/1	0/3	0/3
	48.0	16.0	0/2	0/2	0/2	0/2	0/4	0/4
	96.0	32.0			0/2	0/2	0/2	0/2
				PLASMODIUM VIVAX				
CHESSON	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	2/2	1/2	2/4	1/4
	48.0	16.0	0/2	0/2	1/3	0/3	1/5	0/5
	96.0	32.0			4/5	1/5	4/5	1/5
	192.0	64.0			1/1	0/1	1/1	0/1

TABLE 19

SUMMARY OF THE ACTIVITY OF WR 250531AA (BN: BK 50768) AGAINST INFECTIONS OF ONE STRAIN OF PLASMODIUM FALCIPARUM AND ONE STRAIN OF PLASMODIUM VIVAX

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
				PLASMODIUM FALCIPARUM				
UPA	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	0/2	0/2	0/4	0/4
	48.0	16.0	0/2	0/2	0/2	0/2	0/4	0/4
	96.0	32.0			2/3	1/3	2/3	1/3
				PLASMODIUM VIVAX				
CHESSON	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	1/2	0/2	1/4	0/4
	48.0	16.0	0/2	0/2	3/4	0/4	3/6	0/6
	96.0	32.0			1/3	0/3	1/3	0/3

EVALUATION OF THE ANTIMALARIAL ACTIVITIES OF SIX QUINAZOLINES AND A RE-ASSESSMENT OF WR 158122 AGAINST *PLASMODIUM FALCIPARUM* INFECTIONS

Schmidt (1973, 1978c, 1979a) reported on the antimalarial activity of WR 158122, 2,4-diamino -6-(2-naphthyl)-sulfonylquinazoline against infections of pyrimethamine-sensitive and resistant strain of *P. falciparum*. When administered at a dose of 0.025 mg base per kg and higher for seven consecutive days, infections of the Vietnam Oak Knoll strain (pyrimethamine sensitive) were cured. No infections of the pyrimethamine-resistant Vietnam Smith strain were cured by doses of 0.39 to 25.0 mg base per kg (x 7 days).

This section will summarize the antimalarial activity of WR 158122 when administered for three consecutive days and present the evaluation of six other quinazolines.

A. WR 158122AC (BN: AY 65859)

The data presented in Table 20, indicate that doses from 2.0 through 32.0 mg base per kg (x 3 days) cleared primary parasitemias of the Vietnam Smith strain, however no infections were cured.

Infections of the pyrimethamine-sensitive Vietnam Oak Knoll strain were cured (Table 20) by doses from 0.0312 through 2.0 mg base per kg (x 3 days).

These data indicate that administration of WR 158122 at a total dose for three consecutive days in the Panamanian *Aotus* model is comparable to the results obtained when the total dose is administered in the Colombian *Aotus* model.

B. WR 222448AD (BN: BH 13998)

Evaluation of this quinazoline (Table 21) indicated blood schizonticidal activity against infections of either the Vietnam Smith or Vietnam Oak Knoll strains. Its potential as an antimalarial agent was negated by toxicity, as evidenced by body weight loss of the monkey, and death.

C. WR 226337AB (BN: BG 79026)

As shown in Table 22, 1 of 1 primary infections of the Vietnam Smith strain were cured by a dose of 8.0 mg base per kg (x 3 days), 2 of 3 primary infections were cured by a dose of 16.0 mg base per kg (x 3 days), and 1 of 1 primary infections were cured by a dose of 32.0 mg base per kg (x 3 days). Lower doses, 2.0 and 4.0 mg base per kg (x 3 days) cured primary infections of the Vietnam Oak Knoll strain.

The drug, however, was toxic at curative doses and no additional studies were done.

D. WR 232716AB (BN: BH 78711)

Primary infections of the Vietnam Smith were not cured (Table 23) by doses of 0.25, 1.0, or 4.0 mg base per kg (x 3 days). Parasite clearance was obtained by retreatment at higher, but toxic doses.

Primary and recrudescent infections of the pyrimethamine-sensitive Vietnam Oak Knoll strain were cured uniformly (Table 23) by doses of 0.25 mg base per kg (x 3 days) and higher.

E. WR 150015AC (BN: BH 80257)

Results of the pilot evaluation of this quinazoline are presented in Table 24. Blood schizonticidal activity against infections of the Vietnam Smith strain was apparent at doses of 4.0 and 16.0 mg base per kg (x 3 days). Two of three infections were cured by a dose of 4.0 mg base per kg (x 3 days).

Infections of the Vietnam Oak Knoll strain were cured by doses of 0.125 to 4.0 mg base per kg (x 3 days).

Deaths due to drug toxicity occurred subsequent to the administration of 1.0, 4.0, and 16.0 mg base per kg (x 3 days).

F. WR 150017AC (BN: BH 30097)

As shown in Table 25, WR 150017 cleared parasitemias of the Vietnam Smith strain, but did not cure infections.

Vietnam Oak Knoll infections were cured with a dose of 4.0 or 16.0 mg base per kg (x 3 days).

G. WR 157384AB (BN: BH 96906)

Pilot evaluation of this quinazoline (Table 26) against infections of the Vietnam Oak Knoll strain indicated no curative activity of primary infections by doses of 0.25, 1.0 or 4.0 mg base per kg (x 3 days).

CONCLUSIONS

WR 158122 administered for three consecutive days was as effective against infections of the pyrimethamine-sensitive Vietnam Oak Knoll strain as when administered for seven consecutive days. Cross resistance to the pyrimethamine-resistant Vietnam Smith strain was confirmed.

Two quinazolines, WR 232716 and WR 150015 had activity against infections of the Vietnam Oak Knoll strain, but no drug had blood schizonticidal/curative activity against the Vietnam Smith strain without concomitant drug toxicity.

TABLE 20

SUMMARY OF THE ACTIVITY OF WR 158122AC (BN: AY 65859) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
VIETNAM SMITH	1.5	0.5	0/1	0/1			0/1	0/1
	3.0	1.0	0/1	0/1			0/1	0/1
	6.0	2.0	1/1	0/1			1/1	0/1
	12.0	4.0	1/1	0/1	1/1	0/1	2/2	0/2
	24.0	8.0	1/1	0/1			1/1	0/1
	48.0	16.0	1/1	0/1			1/1	0/1
	96.0	32.0	1/1	0/1			1/1	0/1
	192.0	64.0	0/1	0/1			0/1	0/1
VIETNAM OAK KNOLL	0.0936	0.0312	1/1	1/1			1/1	1/1
	0.1875	0.0625	2/2	2/2			2/2	2/2
	0.375	0.125	1/1	1/1			1/1	1/1
	0.75	0.25	1/1	1/1			1/1	1/1
	1.5	0.5	1/1	1/1			1/1	1/1
	3.0	1.0	1/1	1/1			1/1	1/1
	6.0	2.0	1/1	1/1			1/1	1/1

TABLE 21

SUMMARY OF THE ACTIVITY OF WR 222448AD (BN: BH 13998) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
VIETNAM SMITH	3.0	1.0	0/1	0/1			0/1	0/1
	6.0	2.0	1/1	0/1			1/1	0/1
	12.0	4.0	1/1	Died Day 8 post Rx*			1/1	--
	24.0	8.0	1/1	0/1			1/1	0/1
	48.0	16.0	1/1	0/1			1/1	0/1
	96.0	32.0	1/1	Died Day 4 post Rx*	1/2	Died Day 3, 8* 1/1		--
	192.0	64.0	1/1	Died Day 5 post Rx*			1/1	--
VIETNAM OAK KNOLL	0.1875	0.0625	0/1	0/1			0/1	0/1
	0.75	0.25	0/1	0/1			0/1	0/1
	3.0	1.0	1/1	0/1			1/1	0/1
	6.0	2.0	1/1	0/1	2/2	1/2	3/3	1/3
	12.0	4.0	1/1	0/1	1/1	1/1	2/2	1/2
	24.0	8.0	1/1	1/1	1/3	Died Day 4,4,5,Post Rx*	1/4	1/1
	48.0	16.0	1/1	Died Day 7 post-Rx*			1/1	--

* Drug toxicity

TABLE 22

SUMMARY OF THE ACTIVITY OF WR 226337AB (BN: BG 79026) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
VIETNAM SMITH	3.0	1.0	0/1	0/1			0/1	0/1
	12.0	4.0	1/1	0/1			1/1	0/1
	24.0	8.0	1/1	1/1			1/1	1/1
	48.0	16.0	3/3	2/3			3/3	2/3
	96.0	32.0	3/3	1/1 a)	1/1	b)	4/4	1/1
	192.0	64.0	1/1	c)	1/1	d)	2/2	--
VIETNAM OAK KNOLL	0.0468	0.0156	0/1	0/1			0/1	0/1
	0.1875	0.0625	0/1	0/1			0/1	0/1
	0.75	0.25	0/2	Died-malaria			0/2	--
	3.0	1.0	0/1	0/1			0/1	0/1
	6.0	2.0	3/3	1/2 e)			3/3	1/2
	12.0	4.0	2/2	1/2	2/2	f)	4/4	1/2
	24.0	8.0	2/2	g)	1/1	h)		

a) Two monkeys died Day 4 and 32 post Rx, respectively - drug toxicity

b) Died Day 4 post-Rx - drug toxicity

c) Died Day 26 post-Rx - drug toxicity

d) Died day 32 post-Rx - drug toxicity

e) One died - malaria

f) One died - malaria, one died Day 19 post-Rx, drug toxicity

g) Two died Day 4 post-Rx - drug toxicity

h) Died Day 13 post-Rx - drug toxicity

TABLE 23

SUMMARY OF THE ACTIVITY OF WR 232716AB (BN: BH78711) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
VIETNAM	0.75	0.25	0/1	0/1			0/1	0/1
SMITH	3.0	1.0	0/1	0/1	0/1	0/1	0/2	0/2
	12.0	4.0	1/1	a)	1/2	1/1 b)	1/3	1/1
	24.0	8.0			1/1	0/1	1/1	0/1
	48.0	16.0			1/1	c)	1/1	--
	192.0	64.0			1/1	c)	1/1	--
VIETNAM	0.0936	0.0312	0/1	0/1			0/1	0/1
OAK KNOLL	0.1875	0.0625	1/1	0/1	1/1	0/1	2/2	0/2
	0.375	0.125	2/2	1/2	1/1	0/1	3/3	1/3
	0.75	0.25			1/1	1/1	1/1	1/1
	1.5	0.5	1/1	1/1	2/2	2/2	3/3	3/3
	6.0	2.0	1/1	1/1			1/1	1/1
	12.0	4.0	1/1	1/1			1/1	1/1
	96.0	32.0	1/1	1/1			1/1	1/1

a) Died Day 8 post Rx, drug toxicity

b) One died Day 5 post-Rx, drug toxicity

c) Died Day 8 post-Rx, drug toxicity

TABLE 24

SUMMARY OF THE ACTIVITY OF WR 150015AC (BN: BH 80257) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
VIETNAM SMITH	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	1/2	0/1 a)	2/2	2/2	3/4	2/3
	48.0	16.0	1/2	b)	1/1	c)	2/3	--
VIETNAM OAK KNOLL	0.375	0.125	2/2	2/2			2/2	2/2
	0.75	0.25	2/2	2/2			2/2	2/2
	3.0	1.0	4/4	3/4 d)			4/4	3/4
	12.0	4.0	2/2	1/2 e)			2/2	1/2
	48.0	16.0	1/2	f)			1/2	--

a) One died Day 7 post Rx, drug toxicity

b) Two died - Day 5 and 6 post Rx, respectively - drug toxicity

c) Died Day 4 post-Rx- drug toxicity

d) One died Day 5 post-Rx- drug toxicity

e) One died Day 7 post Rx - drug toxicity

f) Two died Days 5 and 7 post-Rx, respectively - drug toxicity

TABLE 25

SUMMARY OF THE ACTIVITY OF WR 150017AC (BN: BH 30097) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
VIETNAM SMITH	3.0	1.0	0/1	0/1			0/1	0/1
	12.0	4.0	0/2	0/2	1/2	0/2	1/4	0/4
	48.0	16.0	1/2	0/1 a)	3/4	0/2 b)	4/6	0/3
	96.0	32.0			1/3	0/3	1/3	0/3
	192.0	64.0			2/2	0/2	2/2	0/2
	384.0	128.0			2/2	0/2	2/2	0/2
VIETNAM OAK KNOLL	3.0	1.0	2/2	0/2			2/2	0/2
	12.0	4.0	2/2	1/2	2/2	1/1 c)	4/4	2/3
	48.0	16.0	2/2	d)	1/1	1/1	3/3	1/1

a) One died Day 7 post Rx - drug toxicity

b) One died Day 4 post - Rx, trauma
One died Day 12 post-Rx, - drug toxicity

c) One died Day 49 post - Rx - intercurrent infection

d) Two died Day 39 and 41 post Rx, respectively, intercurrent infection

TABLE 26

SUMMARY OF THE ACTIVITY OF WR 157384AB (BN: BH 96906) AGAINST INFECTIONS OF THE VIETNAM OAK KNOLL STRAIN OF *PLASMODIUM FALCIPARUM*

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
OAK KNOLL	0.75	0.25	0/2	0/2			0/2	0/2
	3.0	1.0	0/2	0/2	0/2	0/2	0/4	0/4
	12.0	4.0	1/2	0/2	4/4	1/4	5/6	1/6
	48.0	16.0			5/5	5/5	5/5	5/5

ACTIVITY OF TWO QUINOLINE METHANOLS AGAINST PLASMODIUM FALCIPARUM INFECTIONS

A. WR 226663AA (BN: BG 47211)

One of three primary infections of the multi-resistant Vietnam Smith strain (Table 27) was cured by a dose 8.0 mg base per kg (x 3 days), and 1 of 2 primary infections by a dose of 16.0 mg base per kg (x 3 days). The latter dose cured 2 of 2 recrudescences, and a dose of 32.0 mg base per kg (x 3 days) cured 1 of 1 recrudescences.

B. WR 215440AB (BN: BH 08586)

As indicated in Table 27, a total of 5 of 5 primary and recrudescent infections of the Uganda Palo Alto strain were cured by a dose of 4.0 mg base per kg (x 3 days)

One of two primary Vietnam Smith and 4 of 5 recrudescences infections were cured by a dose of 16.0 mg base per kg (x 3 days). Two of two recrudescences were cured by a dose of 32.0 mg base per kg (x 3 days).

CONCLUSION

Neither of these quinolinemethanols was as effective against Vietnam Smith infections as WR 142490 (mefloquine).

TABLE 27

SUMMARY OF THE ACTIVITY OF TWO QUINOLINEMETHANOLS AGAINST INFECTIONS OF PLASMODIUM FALCIPARUM

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
				WR 226663AA (BN: BG 47211)				
VIETNAM SMITH	6.0	2.0	0/1	0/1			0/1	0/1
	12.0	4.0			1/1	0/1	1/1	0/1
	24.0	8.0	3/3	1/3			3/3	1/3
	48.0	16.0	2/2	1/2	2/2	2/2	4/4	3/4
	96.0	32.0			1/1	1/1	1/1	1/1
				WR 215440AB (BN: BH 08586)				
UGANDA PALO ALTO	0.75	0.25	0/1	0/1	1/1	1/1	1/2	1/2
	3.0	1.0	1/3	0/3	1/2	1/2	2/5	1/5
	12.0	4.0	1/1	1/1	4/4	4/4	5/5	5/5
VIETNAM SMITH	3.0	1.0	0/1	0/1			0/1	0/1
	12.0	4.0	0/1	0/1	0/1	0/1	0/2	0/2
	24.0	8.0	3/4	0/4	1/1	Died Day 64 post Rx	4/5	0/4
	48.0	16.0	2/2	1/2	5/5	4/5	7/7	5/7
	96.0	32.0			2/2	2/2	2/2	2/2

ACTIVITY OF TWO TRIAZINES AGAINST PLASMODIUM FALCIPARUM INFECTIONS

A. WR 169626AA (BN: AX 97007)

Results of a pilot evaluation of WR 169626AA, the hydrochloride salt of an acetylated triazine, against infections of the pyrimethamine-resistant Vietnam Smith strain are shown in Table 28. Primary parasitemias were not cleared by doses of 2.5 or 5.0 mg base per kg (x 3 days). Re-treatment with sequentially higher doses, viz. 5.0 or 10.0 mg base per kg did not clear parasitemias, whereas primary parasitemias were cleared by these doses, indicating a possible acquired resistance to WR 169626AA. One of two primary infections was cured at by a dose of 10.0 mg base per kg (x 3 days).

B. WR 169626AB (BN: BJ57388)

Results of the evaluation of WR 169626AB, free base, against the Vietnam Smith strain and the pyrimethamine-sensitive Vietnam Oak Knoll are summarized in Table 28. Primary Vietnam Smith parasitemias were all cleared by doses of 5.0, 10.0, 20.0, or 40.0 mg base per kg (x 3 days), but no dose cured 100% of the infections. Treatment failures, retreated by doses as high as 160.0 mg base per kg (x 3 days) were not cured uniformly.

Doses of 10.0, 20.0, and 40.0 mg base per kg (x 3 days) cleared primary parasitemias of the Vietnam Oak Knoll strain (Table 28), but did not cure all of the infections. Infections, retreated by doses up to and including 40.0 mg base per kg (x 3 days), were not cured uniformly.

C. WR 169627AA (BN: 41774)

Schmidt (1972) reported on the activity of WR 169627, an acetylated triazine, against infections of the chloroquine-sensitive Malayan Camp-CH/Q and chloroquine-resistant Vietnam Oak Knoll strains of P. falciparum.

Infections of the Malayan Camp-CH/Q strain were cured by doses of 1.25, 2.5,or 5.0 mg base per kg administered for seven consecutive days. Cures of infections of the Vietnam Oak Knoll strain were obtained with doses of 2.5 or 5.0 mg base per kg (x 7 days), however the curative doses were one-half the lethal dose.

WR 169627, administered for three consecutive days, was revaluated in the Panamanian Aotus model (Table 29). Doses of 2.5 mg base per kg (x 3 days) and higher cleared primary parasitemias of the Vietnam Smith strain, while primary infections were cured consistently by a dose of 10.0 or 20.0 mg base per kg (x 3 days). Retreatment with doses of 2.5 to 40.0 mg base per kg (x 3 days) did not consistently clear parasitemias or cure infections. Drug toxicity occurred at doses of 20.0 and 40.0 mg base per kg (x 3 days).

As indicated in Table 29, no primary infections of the Vietnam Oak Knoll strain were cured by doses of 1.25, 2.5, or 5.0 mg base per kg (x 3 days). Retreatment with a dose of 10.0 mg base per kg (x 3 days) cured 2 of 2 infections.

CONCLUSIONS

WR 169626AA had slight anti-malaria activity against infections of the Vietnam Smith strain and may have induced drug resistance during re-treatments.

WR 169627 was more active than WR 169626 against infections of the pyrimethamine-resistant Vietnam Smith strain whereas the latter drug was more active against infections of the pyrimethamine-sensitive Vietnam Oak Knoll strain.

TABLE 28
SUMMARY OF THE ACTIVITY OF WR 169626 AGAINST INFECTIONS
OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
			WR 169626AA (BN: AX 97007)					
VIETNAM	7.5	2.5	1/2	0/2			1/2	0/2
SMITH	15.0	5.0	2/2	0/2	0/2	0/2	2/4	0/4
	30.0	10.0	2/2	1/2	0/3	0/3	2/5	1/5
			WR 169626AB (BN: BJ 57388)					
VIETNAM	7.5	2.5	1/3	0/3			1/3	0/3
SMITH	15.0	5.0	3/3	2/3	1/3	0/3	4/6	2/6
	30.0	10.0	3/3	1/3	1/4	0/4	4/7	1/7
	60.0	20.0	3/3	2/3	4/6	1/5 a)	7/9	3/8
	120.0	40.0	3/3	1/3	5/5	3/5	8/8	4/8
	240.0	80.0			3/4	2/4	3/4	2/4
	480.0	160.0			2/2	1/2	2/2	1/2
VIETNAM	3.75	1.25	0/2	0/2			0/2	0/2
OAK KNOLL	7.5	2.5	0/2	0/2	1/1	0/1	1/3	0/3
	15.0	5.0	1/2	0/2	1/3	0/3	2/5	0/5
	30.0	10.0	2/2	0/2	3/5	1/5	5/7	1/7
	60.0	20.0	2/2	1/2	4/4	1/4	6/6	2/6
	120.0	40.0	2/2	1/2	3/3	2/3	5/5	3/5
	240.0	80.0			1/1	1/1	1/1	1/1

a) One died Day 58 post-Rx-gastric ulcer

TABLE 29

SUMMARY OF THE ACTIVITY OF WR 169627AA (BN: ZN 41744) AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
VIETNAM SMITH	3.75	1.25	0/2	0/2			0/2	0/2
	7.5	2.5	2/2	0/2	0/2	0/2	2/4	0/4
	15.0	5.0	2/2	0/2	2/4	1/4	4/6	1/6
	30.0	10.0	2/2	2/2	4/5	1/5	6/7	3/7
	60.0	20.0	2/2	2/2	3/4	2/3 a)	5/6	4/5
	120.0	40.0			0/1	b)		
VIETNAM OAK KNOLL	3.75	1.25	0/2	0/2			0/2	0/2
	7.5	2.5	0/2	0/2	0/2	0/2	0/4	0/4
	15.0	5.0	2/2	0/1 c)	4/4	1/4	6/6	0/5
	30.0	10.0			3/3	2/2 d)	3/3	2/2

a) One died Day 2 post Rx, gastritis

b) Died Day 4 post Rx, diarrhea

c) Died Day 41 post Rx, anorexia

d) 1 Died Day 15 post-Rx, anorexia

ACTIVITY OF SEVEN ACRIDINES AGAINST PLASMODIUM FALCIPARUM INFECTIONS

The antimalarial properties of floxacrine, [7-chloro-10-hydroxy-3 (4-trifluoromethylphenyl)-3,4-dihydroacridine-1,9(2H,10H)-dione] were reported by Schmidt (1979b). Primary infections of the Vietnam Smith strain were cured by doses of 2.5, 10.0, or 40.0 mg base per kg (x 7 days). The CD_{90} was a total of 154 mg per kg.

A series of seven acridines were evaluated against infections of two strains of P. falciparum in the Panamanian Aotus model.

A. WR 233602AE (BN: BK 15974)

Results of the re-evaluation of floxacrine, administered for three consecutive days, are shown in Table 30. Primary infections of the Uganda Palo Alto strain were not cured by doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days). Retreatment with higher doses did not consistently cure infections.

Doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days) did not clear primary or re-treatment parasitemias of the Vietnam Smith strain.

Retreatment with a dose of 32.0 mg base per kg (x 3 days) cleared parasitemia in 2 of 2 Aotus, but did not cure the infection.

B. WR 235326AB (BN: BH 96362)

Pilot assessment of this acridinone, 7-chloro-3-(3,4-dichlorophenyl) -1-[[3-dimethylamino)-propyl] imino]-1,2,3,4-tetrahydro-9(10H) acridinone indicated no curative activity at doses of 4.0, 8.0, or 16.0 mg base per kg (x 3 days) against primary infections of the Uganda Palo Alto strain(Table 30). Retreatment with higher doses did not consistently clear parasitemia or cure infection.

Vietnam Smith primary infections were not cured by doses of 4.0, 8.0, or 16.0 mg base per kg (x 3 days). Retreatment with doses of 16.0 mg base per kg (x 3 days) and higher cleared parasitemias, but cured infections in only 2 of 13 Aotus.

C. WR 237221AB (BN: BJ 01091)

Results of a pilot assessment of WR 237221, 7-chloro-3-(2,4-dichlorophenyl)-[[3-dimethylamino)propyl] imino] -1,3,4,10-tetrahydro-10-hydroxy -9-(2H)-acridinone are presented in Table 31. One of two primary infections and the infection in 1 of 1 retreated Aotus were cured by a dose of 4.0 mg base per kg (x 3 days). Doses of 8.0 or 16.0 mg base per kg (x 3 days) cured primary infections.

Primary Vietnam Smith infections were uniformly cured by doses of 8.0 and 16.0 mg base per kg (x 3 days).

Neither dose uniformly cured infections in retreated monkeys.

D. WR 237224AA (BN: BH57132)

As shown in Table 31, this drug was inactive, at the doses used, against primary infections of the Uganda Palo Alto and Vietnam Smith strains. The amount of drug available was insufficient for retreatments.

E. WR 237942AB (BN: BH 89652)

Pilot assessment (Table 31) of this acridinedione, 7-chloro-3-(3,4-dichlorophenyl)-3,4-dihydro-10-hydroxy-2-methyl-1,9(2H,10H)- acridinedione used monkeys previously treated with a non-curative drug.

Parasitemias of the Uganda Palo Alto strain were cleared by doses of 1.0, 4.0, or 8.0 mg base per kg (x 3 days). One of two infections each were cured by doses of 1.0 or 4.0 mg base per kg (x 3 days), and 1 of 1 infection by a dose of 8.0 mg base per kg (x 3 days).

Vietnam Smith parasitemias were cleared by doses of 1.0 through 32.0 mg base per kg (x 3 days). One of three and 1 of 2 infections were cured by doses of 8.0 and 16.0 mg base per kg (x 3 days), respectively, and a dose of 32.0 mg base per kg (x 3 days) cured 1 of 1 infection.

F. WR 243251AB (BN: BJ 4573)

The activity of WR 243251, 7-chloro-3-(2,4-dichlorophenyl)-1-[[(3-dimethylamino) propyl] imino] -1,2,3,4-tetrahydro-9(10H) acrinone, is summarized in Table 32. As measured by clearance of primary parasitemias, this drug was equally active against infections of the Uganda Palo Alto and Vietnam Smith strains. Parasitemias of both strains were cleared by doses of 1.0 though 64.0 mg base per kg (x 3 days). All primary infections of either strain were cured by doses of 8.0, 16.0, or 64.0 mg base per kg (x 3 days).

A total of 20 of 22 (91 %) Uganda Palo Alto infections and 19 of 27 (70 %) Vietnam Smith infections were cured. No evidence of drug toxicity was noted.

G. WR 246976AB (BN: BJ 85131)
WR 246976AC (BN: BJ 92190)

The antimalarial assessment of WR 246976AB, 9-chloro-4-(2,4-dichlorophenyl)-4,5-dihydro-3-H-isoxazolo-[3,4,5-kl] acridine is shown in Table 32. Primary parasitemias of the Uganda Palo Alto strain were not cleared by oral doses of 1.0, 2.0, or 4.0 mg base per kg (x 3 days). Retreatment with doses of 2.0, 4.0, or 8.0 mg base per kg (x 3 days) also were ineffective in parasite clearance. While doses of 16.0 mg base per kg (x 3 days) and higher cleared parasitemias, only 3 of 6 infections were cured.

Because of the relative inactivity of this drug when administered orally, the drug (WR 249676AC) was administered intramuscularly to each of two Aotus infected with the Uganda Palo Alto strain (Table 32). The infection in one Aotus was cured by a dose of 8.0 mg base per kg (x 3 days), and in the other monkey by a dose of 32.0 mg base per kg (x 3 days).

Oral administration of WR 246976AB was equally ineffective in curing infections of the Vietnam Smith strain (Table 32). Only one infection in a total of 19 Aotus was cured.

CONCLUSION

One of these acridines, WR 243251, had greater antimalarial activity than floxacrine (WR 233602) against infections of P. falciparum in Aotus. A dose of 1.0 mg base per kg (x 3 days) cured infections of the Uganda Palo Alto strain, and a dose of 4.0 mg base per kg (x 3 days) cured 3 of 4 Vietnam Smith infections.

TABLE 30

SUMMARY OF THE ACTIVITY OF TWO ACRIDINES AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
				WR 233602AE (BN: BK 15974)				
UGANDA	3.0	1.0	0/2	0/2			0/2	0/2
PALO ALTO	12.0	4.0	0/2	0/2	1/3	1/3	1/5	1/5
	48.0	16.0	0/2	0/2	3/4	2/4	3/6	2/6
	96.0	32.0			4/4	1/3 a)	4/4	1/3
	192.0	64.0			1/1	0/1	1/1	0/1
VIETNAM	3.0	1.0	0/2	0/2			0/2	0/2
SMITH	12.0	4.0	0/2	0/2	0/2	0/2	0/4	0/4
	48.0	16.0	0/2	0/2	0/2	0/2	0/4	0/4
	96.0	32.0			2/2	0/2	2/2	0/2
				WR 235326AB (BN: BH 96362)				
UGANDA	12.0	4.0	1/2	0/1 b)			1/2	0/1
PALO ALTO	24.0	8.0	0/2	0/2	1/1	0/1	1/3	0/3
	48.0	16.0	0/2	0/2	2/3	1/3	2/5	1/5
	96.0	32.0			2/3	0/3	2/3	0/3
	192.0	64.0			2/2	0/2	2/2	0/2
VIETNAM	12.0	4.0	0/2	0/2			0/2	0/2
SMITH	24.0	8.0	0/2	0/2	1/2	0/2	1/4	0/4
	48.0	16.0	1/2	0/2	4/4	1/4	5/6	1/6
	96.0	32.0			4/4	0/4	4/4	0/4
	192.0	64.0			2/2	1/2	2/2	1/2
	384.0	128.0			1/1	0/1	1/1	0/1

a) 1 died Day 15 post Rx, anorexia

b) 1 died Day 11 post Rx, trauma

TABLE 31

SUMMARY OF THE ACTIVITY OF THREE ACRIDINES AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
				WR 237221AB (BN: BJ 01091)				
UGANDA	6.0	2.0	1/2	0/2			1/2	0/2
PALO ALTO	12.0	4.0	2/2	1/2	1/1	1/1	3/3	2/3
	24.0	8.0	2/2	2/2	1/1	1/1	3/3	3/3
	48.0	16.0	2/2	2/2			2/2	2/2
VIETNAM	12.0	4.0	2/2	0/2			2/2	0/2
SMITH	24.0	8.0	2/2	2/2	2/2	1/2	4/4	3/4
	48.0	16.0	2/2	2/2	1/1	0/1	3/3	2/3
				WR 237224AA (BN: BH 57132)				
UGANDA	12.0	4.0	0/2	0/2			0/2	0/2
PALO ALTO	24.0	8.0	0/2	0/2			0/2	0/2
	48.0	16.0	0/2	0/2			0/2	0/2
VIETNAM	12.0	4.0	0/2	0/2			0/2	0/2
SMITH	24.0	8.0	0/2	0/2			0/2	0/2
	48.0	16.0	0/2	0/2			0/2	0/2
				WR 237942AB (BN: BH 89652)				
UGANDA	3.0	1.0			2/2	1/2	2/2	1/2
PALO ALTO	12.0	4.0			2/2	1/2	2/2	1/2
	24.0	8.0			1/1	1/1		
VIETNAM	3.0	1.0			1/1	0/2	1/2	0/2
SMITH	12.0	4.0			3/3	0/3	3/3	0/3
	24.0	8.0			2/3	1/3	2/3	1/3
	48.0	16.0			2/2	1/2	2/2	1/2
	96.0	32.0			1/1	1/1	1/1	1/1

TABLE 32

SUMMARY OF THE ACTIVITY OF TWO ACRIDINES AGAINST INFECTIONS OF TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
				WR 243251AB (BN: BJ 4573)				
UGANDA PALO ALTO	3.0	1.0	2/2	2/2			2/2	2/2
	6.0	2.0	2/2	1/2	1/2	1/2	3/4	2/2
	12.0	4.0	4/4	3/4	2/2	1/2	6/6	4/6
	24.0	8.0	4/4	4/4	2/2	2/2	6/6	6/6
	48.0	16.0	4/4	4/4			4/4	4/4
	192.0	64.0	2/2	2/2			2/2	2/2
VIETNAM SMITH	3.0	1.0	2/2	0/2			2/2	0/2
	6.0	2.0	2/2	0/2	2/2	1/2	4/4	1/4
	12.0	4.0	4/4	3/4	4/4	3/4	8/8	6/8
	24.0	8.0	4/4	4/4	1/1	0/1	5/5	4/5
	48.0	16.0	4/4	4/4	2/2	2/2	6/6	6/6
	192.0	64.0	2/2	2/2			2/2	2/2
				WR 246976AB (BN: BJ 85131)				
UGANDA PALO ALTO	3.0	1.0	0/2	0/2			0/2	0/2
	6.0	2.0	0/2	0/2	0/2	0/2	0/4	0/4
	12.0	4.0	0/2	0/2	0/2	0/2	0/4	0/4
	24.0	8.0			0/2	0/2	0/2	0/2
	48.0	16.0			2/2	0/2	2/2	0/2
	96.0	32.0			3/3	2/3	3/3	2/3
	192.0	64.0			3/3	1/3	3/3	1/3
	384.0	128.0			1/1	0/1	1/1	0/1
	24.0	8.0*	2/2	1/2			2/2	1/2
	48.0	16.0*			1/1	0/1	1/1	0/1
	96.0	32.0*			1/1	1/1	1/1	1/1
VIETNAM SMITH	3.0	1.0	0/2	0/2			0/2	0/2
	6.0	2.0	0/2	0/2	0/2	0/2	0/4	0/4
	12.0	4.0	0/2	0/2	0/2	0/2	0/4	0/4
	24.0	8.0			0/2	0/2	0/2	0/2
	48.0	16.0			2/2	1/2	2/2	1/2
	96.0	32.0			2/2	0/2	2/2	0/2
	192.0	64.0			2/2	0/2	2/2	0/2
	384.0	128.0			1/1	0/1	1/1	0/1

* Intramuscular WR 246976AC (BN: BJ 92190)

ACTIVITY OF TWO ACRIDINOLS AGAINST INFECTIONS OF PLASMODIUM FALCIPARUM AND PLASMODIUM VIVAX

A. WR 250547AA (BN: BK 51630)

Results of the pilot evaluation of WR 250547 are given in Table 33. Primary infections of the Vietnam Smith strain of P. falciparum were cured by doses of 1.0, 4.0, and 16.0 mg base per kg (x 3 days).

One of two primary infections of P. vivax (Chesson strain) were cured by a dose of 1.0 mg base per kg (x 3 days), 1 of 1 infection cured by a dose of 4.0 mg base per kg (x 3 days), and 1 of 2 infections cured by a dose of 16.0 mg base per kg (x 3 days).

B. WR 250548AA (BN: BK 51621)

No primary infections (Table 33) of P. falciparum (Vietnam Smith strain) were cured by doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days). A total of 4 of 17 infections were cured, but only by multiple retreatment.

At the doses used, this drug had no blood schizonticidal activity against blood-induced P. vivax infections.

CONCLUSIONS

WR 250547 was active against *P. falciparum* and *P. vivax* infections. Cures were obtained by a dose of 1.0 mg base per kg (x 3 days). Additional studies are in progress.

TABLE 33

SUMMARY OF THE ACTIVITY OF TWO ACRIDINOLS AGAINST INFECTIONS OF PLASMODIUM FALCIPARUM AND PLASMODIUM VIVAX

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
WR 250547AA (BN: BK 51630)								
P. FALCIPARUM								
VIETNAM SMITH	3.0	1.0	2/2	1/2			2/2	1/2
	12.0	4.0	2/2	2/2	1/1	1/1	3/3	3/3
	48.0	16.0	2/2	2/2			2/2	2/2
P. VIVAX								
CHESSON	3.0	1.0	1/2	1/2			1/2	1/2
	12.0	4.0	2/2	1/1 a)	1/1	1/1	3/3	2/2
	48.0	16.0	1/2	1/2			1/2	1/2
	192.0	64.0			1/1	1/1	1/1	1/1
WR 250548AA (BN: BK 51621)								
P. FALCIPARUM								
VIETNAM SMITH	3.0	1.0	0/1	0/1			0/1	0/1
	12.0	4.0	0/2	0/2	2/2	0/2	2/4	0/4
	48.0	16.0	2/2	0/2	3/4	2/4	5/6	2/6
	96.0	32.0			1/1	1/1	1/1	1/1
	192.0	64.0			2/3	1/3	2/3	1/3
	384.0	128.0			2/2	0/2	2/2	0/2
P. VIVAX								
CHESSON	3.0	1.0	0/2	0/1 b)			0/2	0/1
	12.0	4.0	0/2	0/1 b)			0/2	0/1
	48.0	16.0	0/2	0/2			0/2	0/2

a) 1 Died day 32 post-Rx, intercurrent infection

b) 1 Died day 5 post-Rx, intercurrent infection

ACTIVITY OF EIGHT DRUGS OF DIVERSE CHEMICAL CLASSES AGAINST PLASMODIUM FALCIPARUM INFECTIONS

A. WR 181613AB (BN: BG61110)

This naphthalene-methanol (Table 34), had no activity, at doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days), against primary infections of the Uganda Palo Alto strain. Multiple retreatments cured 5 of 30 infections. A dose of 128.0 mg base per kg (x 3 days) cured 2 of 4 infections.

No primary Vietnam Smith infections were used in this component of the evaluation. Multiple retreatments cured only 2 of 19 infections.

B. WR 206891AB (BN: BG 47462)

As summarized in Table 34, this pteridineamine, 6-[[(4-chlorophenyl)(1-methylethyl)amino] methyl] -2,4- pteridineamine, had no activity against primary Vietnam Smith infections. Retreatment with doses of 4.0 or 16.0 mg base kg (x 3 days) each cured 1 of 3 infections.

At doses of 1.0 through 128.0 mg base per kg (x 3 days), this drug did not cure Vietnam Oak Knoll infections.

C. WR 229049AC (BN: BH14011)

This pyrolidine, 3,3'-dialkyl- 4,4'-dihydroxy-5,5'(pyrrolidinomethyl) biphenyl dihydrochloride did not cure primary infections of the Uganda Palo Alto strain (Table 35). Retreatment with dose of 64.0 mg base per kg (x 3 days) cured 1 of 1 infection.

D. WR 231010AL (BN: BK 46371)

Results of the pilot evaluation of this thiosemicarbazone are shown in Table 35. The drug had no blood schizonticidal/curative activity against primary Uganda Palo Alto infections. Retreatment by a dose of 32.0 mg base per kg (x 3 days) cured 1 of 4 infections and a dose of 64.0 mg base per kg (x 3 days) cured 1 of 2 infections.

The drug was wholly ineffective against infections of the Vietnam Smith strain. Parasite clearance was not obtained by the doses used.

E. WR 235591AF (BN: BK 50115)

WR 235591, a thiosemicarbazone, was evaluated against infections of the Uganda Palo Alto and Vietnam Smith strains (Table 35). Doses of 1.0 and 4.0 mg base per kg (x 3 days) had no blood schizonticidal activity against primary parasitemias of the Uganda Palo Alto strain. A dose of 16.0 mg base per kg (x 3 days) cleared 1 of 2 primary parasitemias and retreatment by a dose of 32.0 mg base per kg (x 3 days) cleares 2 of 4 parasitemias, and cured 1 of 4 infections.

At the doses used, this drug had no blood schizonticidal or curative

activity against infections of the Vietnam Smith strain.

F. WR 249696AB (BN: BK 45981)

Summary of the pilot evaluation of WR 249696, 3,8-dichloro-N,N-diethyl-11 H-indolo (3,2-C) quinoline-11-ethanamine-5 oxide hydrate, is presented in Table 36. Doses of 1.0 or 4.0 mg base per kg (x 3 days) had no blood schizonticidal activity against primary Uganda Palo Alto infections; 1 of 2 primary parasitemias was cleared only by a dose of 16.0 mg base per kg (x 3 days). Retreatment with a dose of 16.0 mg base per kg (x 3 days) cured 1 of 6 infections, and 1 of 3 infections was cured by a dose 32.0 mg base per kg (x 3 days).

Only 1 of 2 primary Vietnam Smith parasitemias was cleared by a dose of 16.0 mg base per kg (x 3 days). No infections were cured, however.

G. WR 247705AB (BN: BK 57098)

This quinoline was evaluated against Vietnam Smith infections (Table 36). Primary parasitemias were cleared by doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days). Only the latter dose cured primary infections, as well as retreated infections, as well as retreated infections. Retreatment by a dose of 4.0 mg base per kg (x 3 days) cured of 1 of 4 infections.

H. WR 079520AB (BN: BK 70813)

WR 079520 is desferrioxamine (DF), an iron specific chelating agent. Pollack (personal communication) found that in vitro it completely inhibited the growth of P. falciparum. Three experiments have evaluated DF against P. falciparum infections (Uganda Palo Alto strain) in Aotus monkeys. Since this agent is poorly absorbed after oral administration, DF was delivered via ALZET^{R} osmotic pumps, inserted subcutaneously. Each pump contained 2ml of a 200 mg per ml solution of DF.

The results of these studies will be summarized as follows:

Expt. I. One pump was implanted into each of two Aotus. Parasitemia was suppressed in both hosts. One monkey died on day 5 after pump insertion of intercurrent infection. The other animal died on day 7, following pump implantation, with evidence of hepatotoxic reaction to DF.

Expt. II. Each of three Aotus were implanted with one pump, containing DF. Parasitemia was suppressed in 2 of 3 Aotus.

Expt. III. This study is in progress. On day 2 after parasite inoculation, one pump with DF was implanted into each of four Aotus. Parasitemia was suppressed in 3 of 4 monkeys. On post-inoculation day 9, the pumps were removed and a new pump inserted into each of two Aotus.

On post-inoculation day 2, one pump with DF was inserted into each of two Aotus. Additionally, these monkeys were injected subcutaneously with Df at a dose of 30.0 mg base per kg, twice daily, for 10 consecutive days.

The parasitemia in one monkey was cleared by day 4 after initiation of treatment, while the parasitemia in the other Aotus was depressed significantly the maximum parasitemia was 5,000 per cmm vs 2,000,000 in the untreated control.

Each of two Aotus were injected subcutaneously, twice daily, with DF at a dose of 30.0 mg base per kg for 10 consecutive days. The parasitemia was not suppressed.

CONCLUSION

None of the first seven drugs had blood schizonticidal or curative activity against P. falciparum infections to warrant further evaluation.

The in vivo activity of deferrioxamine, WR 079520, did not correspond with its significant activity in-vitro. When delivered via osmotic pump to Aotus infected with P. falciparum, parasitemias in 7 of 9 monkeys were suppressed only. Desferrioxamine, in a combination administration via pump and subcutaneous injection cleared parasitemia in one monkey and significantly suppressed parasitemia in another monkey.

TABLE 34

SUMMARY OF THE ACTIVITY OF DRUGS OF DIVERSE CHEMICAL CLASSES AGAINST PLASMODIUM FALCIPARUM INFECTIONS

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
				WR 181613AB (BN: BG 61110)				
UGANDA PALO ALTO	3.0	1.0	0/2	0/2	1/1	0/1	1/3	0/3
	12.0	4.0	0/2	0/2	1/4	0/4	1/6	0/6
	48.0	16.0	0/2	0/2	3/5	2/5	3/7	2/7
	96.0	32.0			1/5	0/5	1/5	0/5
	192.0	64.0			3/5	1/5	3/5	1/5
	384.0	128.0			4/4	2/4	4/4	2/4
VIETNAM SMITH	3.0	1.0			1/1	0/1	1/1	0/1
	12.0	4.0			2/3	0/3	2/3	0/3
	48.0	16.0			3/5	1/5	3/5	1/5
	96.0	32.0			2/5	1/5	2/5	1/5
	192.0	64.0			4/4	0/3 a)	4/4	0/3
	384.0	128.0			1/2	0/2	1/2	0/2
				WR 206891AB (BN: BG 47462)				
VIETNAM SMITH	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	1/1	1/1	1/3	1/3
	48.0	16.0	0/2	0/2	1/1	1/1	1/3	1/3
VIETNAM OAK KNOLL	3.0	1.0	0/2	0/1 b)			0/2	0/1
	12.0	4.0	0/2	0/2	0/1	0/1	0/3	0/3
	48.0	16.0	0/2	0/2	1/2	0/1 c)	1/4	0/3
	96.0	32.0			2/3	0/2 d)	2/3	0/2
	192.0	64.0			0/1	0/1	0/1	0/1
	384.0	128.0			0/1	0/1	0/1	0/1

a) 1 Died Day 30 post-Rx, intercurrent injection

b) 1 Died day 4 post-Rx, malaria

c) 1 Died day 7 post-Rx, anorexia

d) 1 Died day 12 post-Rx, intercurrent infection

TABLE 35

SUMMARY OF THE ACTIVITY OF DRUGS OF DIVERSE CHEMICAL CLASSES AGAINST PLASMODIUM FALCIPARUM INFECTIONS

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
				WR 229049AC (BN: BH 14011)				
UGANDA PALO ALTO	12.0	4.0	0/2	0/2			0/2	0/2
	48.0	16.0	0/2	0/2	0/1	0/1	0/3	0/3
	192.0	64.0	0/2	0/2	1/1	1/1	1/3	1/3
	384.0	128.0			2/2	0/2	2/2	0/2
				WR 231010AL (BN: BK 46371)				
UGANDA PALO ALTO	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	0/2	0/2	0/4	0/4
	48.0	16.0	0/2	0/2	1/4	0/4	1/6	0/6
	96.0	32.0			1/4	1/4	1/4	1/4
	192.0	64.0			1/2	1/2	1/2	1/2
	384.0	128.0			0/1	0/1	0/1	0/1
VIETNAM SMITH	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	0/2	0/2	0/4	0/4
	48.0	16.0	0/2	0/2	0/3	0/3	0/5	0/5
	96.0	32.0			0/4	0/2 a)	0/4	0/2
	192.0	64.0			0/1	0/1	0/1	0/1
				WR 235591AF (BN: BK 50115)				
UGANDA PALO ALTO	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	0/2	0/1 b)	0/4	0/3
	48.0	16.0	1/2	0/2	0/3	0/3	1/5	0/5
	96.0	32.0			2/4	1/4	2/4	1/4
VIETNAM SMITH	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	0/2	0/2	0/2	0/2	0/4	0/4
	48.0	16.0	0/2	0/2	0/3	0/3	0/5	0/5
	96.0	32.0			0/3	0/2 c)	0/3	0/2

a) 2 died day 4 post-Rx, malaria

b) 1 died day 2 post-Rx, malaria

c) 1 died day 1 post-Rx, malaria

TABLE 36

SUMMARY OF THE ACTIVITY OF TWO QUINOLINES AGAINST INFECTIONS OF PLASMODIUM FALCIPARUM

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
			WR 249696AB (BN: BK 45981)					
UGANDA	3.0	1.0	0/2	0/2			0/2	0/2
PALO ALTO	12.0	4.0	0/2	0/2	1/2	0/2	1/4	0/4
	48.0	16.0	1/2	0/2	4/4	1/4	5/6	1/6
	96.0	32.0			2/3	1/3	2/3	1/3
VIETNAM	3.0	1.0	0/2	0/2			0/2	0/2
SMITH	12.0	4.0	0/2	0/2	0/2	0/2	0/4	0/4
	48.0	16.0	1/2	0/2	0/4	0/4	1/6	0/6
			WR 247705AB (BN: BK 57098)					
VIETNAM	3.0	1.0	2/2	0/2			2/2	0/2
SMITH	12.0	4.0	2/2	0/2	2/2	1/2	4/4	1/4
	48.0	16.0	2/2	2/2	3/3	3/3	5/5	5/5

REFERENCES

Davidson, D. E., Jr. Ager, A. L., Brown, J. L. Chapple, F. E., Whitmire, R. E., and Rossan, R. N. 1981. New tissue schizontocidal antimalarial drugs. Bull. W. H. O. 59: 463-479.

Earle, W. C. and Perez, M. 1931. Enumeration of parasites in the blood of malarial patients. J. Lab. Clin. Med. 17: 1124-1130.

Moore, D. V. and Lanier, J. E. 1961. Observations on Two Plasmodium falciparum infections with an abnormal response to chloroquine. Am. J. Trop. Med. Hyg. 10: 5-9.

Schmidt, L. H. 1972. The use of Aotus trivirgatus as a tool for studies on the therapy of infections with Plasmodium falciparum. Annual Progress Report, Army Contract DADA 17-69-C-9104.

Schmidt, L. H. 1973. Infections with Plasmodium falciparum and Plasmodium vivax in the owl monkey - model systems for basic biological and chemotherapeutic studies. Trans. Roy Soc. Trop. Med. Hyg. 67: 446-474.

Schmidt, L. H., Vaughan D., Mueller, D., Crosby, R. and Hamilton, R. 1977. Activities of various 4-aminoquinolines against infections with chloroquine-resistant strains of Plasmodium falciparum. Antimicrob. Agents Chemoth. 11: 826-843.

Schmidt, L. H. 1978a. Plasmodium falciparum and Plasmodium vivax infections in the owl monkey (Aotus trivirgatus) I. The courses of untreated infections. Am. J. Trop. Med. Hyg. 27: 671-702.

Schmidt, L. H. 1978b. Plasmodium falciparum and Plasmodium vivax infections in the owl monkey (Aotus trivirgatus) II. Responses to chloroquine, quinine and pyrimethamine. Am. J. Trop. Med. Hyg. 27: 703-717.

Schmidt, L. H. 1978c. Plasmodium falciparum and Plasmodium vivax infections in the owl monkey (Aotus trivirgatus) III. Methods employed in the search for new blood schizontocidal drugs. Am. J. Trop. Med. Hyg. 27: 718-737.

Schmidt, L.H., Crosby, R., Rosco, J. and Vaughn, D. 1978d. Antimalarial activities of various 4-quinolinemethanols with special attention to WR-142, 490 (mefloquine). Antimicrob. Agents Chemoth. 13: 1011-1030.

Schmidt, L. H. 1979a. Studies on the 2,4-diamino-6-substituted quinazolines II. Activities of selected derivatives against

infections with various drug-susceptible and drug-resistant strains of Plasmodium falciparum and Plasmodium vivax in owl monkeys. Am. J. Trop. Med. Hyg. 28: 793-807.

Schmidt, L. H. 1979b. Antimalarial properties of floxacrine, a dihydroacridinedione derivative. Antimicrob. Agents Chemother. 16: 475-485.

Young, M. D. 1961. Amodiaquine and hydroxchloroquine resistance in Plasmodium falciparum. Am. J. Trop. Med. Hyg. 10: 689-693.

BIBLIOGRAPHY

Rossan, R. N., Harper, J. S. III, Davidson D. E. Jr., Escajadillo, A. and Christensen H. A. Comparison of Plasmodium falciparum infections in Panamanian and Colombian Aotus monkeys. Submitted to Am. J. Trop. Med. Hyg.

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