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13. ABSTRACT (Maximum 200 words)

The Panamanian Aotus - Plasmodium falciparum model was used to evaluate potential antimalarial drugs; additionally, an Aotus-adapted P. vivax strain was tested for its susceptibility to chloroquine. A water-soluble form of WR 268668, a bisoquinoline was ineffective against Vietnam Smith/RE infections. Two trioxanes (WR 279137 and WR 279138) and a tetroxane (WR 148999) cured infections at doses equivalent to arteether (WR 255131) used as a positive drug control for these experiments. Infections of the Singleton strain of P. vivax were cured by doses of chloroquine that routinely cure such infections, showing that these parasites did not demonstrate a resistance to chloroquine. In a third trial to reverse chloroquine resistance in vivo (Smith/RE infections), a loading dose of chloroquine was followed eight hours later with a dose of promethazine. Primary treatments only suppressed parasitemias while re-treatments at 2x the respective primary dose cleared parasitemias. Post treatment blood film examination to ascertain infection cure is in progress.

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FOREWORD

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Richard N Bossin 23 March 1993

PI Signature Date

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TABLE OF CONTENTS

TABLE OF CONTENTS (CONT'D.)

INTRODUCTION

The essence of the problem addressed in this report is to evaluate the potential antimalarial activity of drugs in the preclinical model of Aotus lemurinus lemurinus (Panamanian night monkey) experimementally infected with Plasmodium falciparum. Such studies with this model were initiated in 1976 at Gorgas Memorial Laboratory, Panama and supported, in part, by the U.S. Army Medical Research and Development Command. Due to the drug resistance exhibited by the highly pathogenic P. falciparum parasites in Asia, Africa, and Latin America, it is essential that new drugs be evaluated in the preclinial Aotus model for their potential usefulness against human infections.

Initially, antimalarial drug studies used the Colombian Aotus as the experimental host (1,2). In the mid 1970's embargoes imposed by South American countries on the exportation of monkeys seriously restricted the use of Aotus for biomedical research in the United States. Panamanian Aotus were available at Gorgas Memorial Laboratory, Panama, and the project transferred here in 1976. Diverse avenues of research have been pursued in attempts to identify effective new antimalarial drugs. Three strains of P. falciparum, Vietnam Smith, Uganda Palo Alto, and Vietnam Oak Knoll, had been adapted to Panamanian Aotus. These strains exhibit diverse susceptibility and/or resistance to standard antimalarial agents. The course of untreated infections in Panamanian Aotus has been characterized and compared with that in Aotus of Colombia (3). Overall, the virulence of these strains was less in Panamanian than in Colombian owl monkeys, as indicated by lower mortality rates of Panamanian monkeys during the first 30 days of patency. Maximum parasitemias of the Vietnam Smith and Uganda Palo Alto strains were, however, significantly higher during the first 15 days of patency in Panamanian than in Colombia owl monkeys. These quantitative differences in infection parameters between Panamanian and Colombian owl monkeys have not invalidated the use of the former for the evaluation of new antimalarial drugs.

Numerous candidate antimalarial drugs of diverse chemical classes have been evaluated against trophozoite-induced infections of one or more P. falciparum strains during the course of these contracts. In seeking alternatives to primaquine, two 8-aminoquinolines proved to be active against the blood stages of P. falciparum (4,5). Desferrioxamine, an iron-specific chelating agent, was shown to suppress parasitemias of the virulent Uganda Palo Alto strain of P. falciparum (6). The in vitro activity of two halogenated histidine analogs was not confirmed by evaluation against P. falciparum infections in owl monkeys (7).

Chloroquine-resistance of P. falciparum represents the greatest challenge in developing effective antimalarial drugs. Reversal of chloroquine-resistance in P. falciparum, in vitro, was achieved by the co-administration of verapamil (a calcium channel blocker) plus

chloroquine (8). Other in vitro studies have shown that there is a significantly greater efflux of chloroquine from erythrocytes containing falciparum parasites resistant to chloroquine than from red cells parasitized by chloroquine-sensitive falciparum malaria (9). Calcium channel blockers appear to prevent this active efflux of chloroquine, thus allowing the drug to accumulate to parasiticidal levels.

Based upon the success of in vitro reversal of chloroquine-resistance, trials were initiated to determine if resistance could be reversed in Aotus infected the chloroquine-resistant Vietnam Smith strain of P. falciparum. Six calcium channel blockers, or similarly acting drugs, were co-administered with chloroquine in diverse regimens. The desideratum of chloroquine-resistance reversal was administration of a single course of treatment, with parasite clearance and infection cure. Suppression of parasitemia was obtained during an initial course of treatment, but parasite clearance and cure occurred in some instances only after re-treatment. Such infection parameters were similarly to those in monkeys with self-limited infections and cure could be attributed to acquired immunity.

Limited trials with desipramine, Norpramin, a tricyclic psychotropic drug, demonstrated the feasibility of reversing chloroquine-resistance in vivo (10). Parasite clearance was obtained, but the infection was not cured.

Subsequently, in vivo reversal of chloroquine resistance was obtained with combinations of chloroquine plus chlorpromazine or prochlorperazine. Such reversal was exhibited by rapid suppression and clearance of parasitemia, resulting in infection cure without retreatment (11).

Evaluation of two oil-soluble derivatives of artemisinin, artemether and arteether, demonstrates that both possess similar activity to cure infections of a multi-drug resistant P. falciparum strain in Aotus.

Both the purpose and methods of approach of the present work remains essentially unchanged since 1976, viz to ascertain the anti-malarial activity of drugs against P. falciparum infections in Aotus. The method of approach may vary on an ad hoc basis, such as administering a combination of drugs.

BODY

I. Experimental Methods

The general intent of this project is to evaluate the potential antimalarial activity of drugs, or combination thereof, in the preclinical model of Aotus experimentally infected with P. falciparum (or P. vivax). Specifically, the vertebrate host is Aotus lemurinus lemurinus, the Panamanian night monkey. These animals are either feral, laboratory adapted or laboratory born. No naturally acquired, human plasmodium infection has been reported in Aotus. The Vietnam Smith/RE strain of P. falciparum was adapted to Aotus of Colombian origin in 1971 (1) and in Panamanian Aotus in 1976.(3) The course of untreated infections, essential for comparison with treated infections, has been documented in Panamanian Aotus (3). This plasmodium strain is resistant to maximally tolerated doses of chloroquine, pyrimethamine, and quinine (2).

To initiate an experiment, infected blood (with 2.5% sodium citrate as the anticoagulant) from an untreated Aotus was diluted appropriately in chilled saline (0.85%), such that each milliliter contained 5,000,000 parasites. This amount was inoculated into the saphenous vein of experimental and control monkeys.

Blood films, prepared and examined daily beginning on the first post-inoculation day, were stained with Giemsa. Parasitemias were evaluated as follows: negative, if no parasites were detected on a thick blood film after examination for at least 5 minutes; <10 parasites per cmm, if positive only on the thick blood film; parasite enumeration was by the Earle-Perez method and reported as the number of parasites per cmm. (12)

Blood films from untreated Aotus, serving as passage and/or control subjects, were prepared and examined daily during the primary patent period, and daily thereafter for at least three consecutive days after parasites could last be detected on thick blood films. When parasitemia had cleared, films were made and examined twice weekly until a total of 100 negative days had been recorded. If a recrudescence occurred, blood films were obtained again on a daily basis.

Parasitemias were evaluated daily during the treatment period and until blood films were negative for at least seven consecutive days. The frequency of smearing was then reduced to two time per week (Monday and Thursdays or Tuesdays and Fridays). If no recrudescences occurred during a 100 day examination period, the infection was considered to have been cured.

Drug doses were calculated as mg base per kg of body weight. Stock solutions of water soluble compounds, at appropriate concentrations, were prepared with distilled water and stored at 8°C for the treatment period. If a compound was water insoluble, a

suspension of the requisite amount of drug was prepared daily with 0.3% methylcellulose (in distilled water).

Oral administration of drugs was by gastric intubation with a 14 French catheter. The total volume of fluid administered, drug solution or suspension, and rinse was 14 ml.

II. Results

A. WR 268668AE(BN:BM 11930)

In the previous annual report (1 May 1991 - 28 Feb. 1992) for this contract, data were presented for the evaluation of WR 268668AC(BM 10586), a water insoluble bisquinoline. In this form, the drug was inactive against Vietnam Smith/RE infections in Aotus, but was active in vitro and in the rodent malaria model. A water soluble methylsulfonate salt was formulated and subsequently evaluated in the monkey model. Initial treatments were by the oral route and retreatments administered intramuscularly. Detailed parasite response is presented in Table 1 and summarized in Table 2. Initial or oral administration of the drug at doses of 2.0, 8.0, and 32.0 mg/kg (x 3 days) only suppressed parasitemias.

Because of the ineffectiveness of the drug by the oral route, retreatments were administered intramuscularly, the drug being dissolved in 5% dextrose solution. Infections in 12639rr and 12643rr were cured. Intramuscular administration of the drug produced severe muscle abscess at the injection site and four animals died of pathogenic sequelae.

B. WR 279137AA(BN:BM 12115), trioxane
WR 279138AA(BN:BM 12124), trioxane
WR 148999AC(BN:BM 11681), tetroxane

These newly synthesized drugs were highly active in vitro and in the mouse malaria model and submitted for pilot evaluation against infections of the Vietnam Smith/RE strain. All drugs were dissolved in sesame oil and administered intramuscularly, 3 doses, at 12 hr intervals, 8:00AM, 8:00PM, and 8:00AM.

Prior to initiation of the pilot evaluation, a toxicity evaluation of WR 148999AC used a malaria-cured Aotus, administered three 144.0 mg/kg doses. No overt adverse reactions were observed and as shown in Table 4, there was no body weight loss, indicating the monkey tolerated this drug dose.

Detailed parasite response to WR 279137AA is shown in Table 5 and summarized in Table 6. Parasitemias were cleared in 2 of 2 Aotus administered three 12.0 mg/kg doses, with a recrudescence in one animal. Three 48.0 mg/kg doses of WR 279137AA cured infections.

Arteether (WR 255131AE; BL 48816) was included in this pilot evaluation as a positive drug control. A dose of 48.0 mg/kg (x3) cured the infections in each of two monkeys.

Data in Tables 7 and 8 indicate that a 12.0 mg/kg (x3) dose of WR 279138AA only suppresses parasitemia. When administered at a dose of 48.0 mg/kg (x3) as a primary or re-treatment, cured infection in 4 of 4 Aotus.

Detailed parasite response to WR 148999AC, a tetroxane, is shown in Table 9 and summarized in Table 10. Doses of 32.0 mg/kg (x3) and 144.0 mg/kg (x3) cured infections following primary treatment.

The activities of the two trioxanes and tetroxane, plus arteether, are summarized in Table 11.

C. WR 1544BM(BN:AR 20613), chloroquine

The identification of P. vivax strains less susceptible to or resistant to previously effective chloroquine regimens prompted the following study. A patient, infected with a P. vivax infection acquired in Panama, received a putative curative regimen of chloroquine and primaquine. A relapse occurred, curative treatment given again, which was followed by a second relapse and treatment. During the first relapse, infected blood was inoculated into an Aotus, previously cured of a P. falciparum infection. The Singleton strain of P. vivax was adapted to Aotus by serial blood passage, and at the seventh passage, an experiment initiated to test the response of these parasites to chloroquine.

The results are detailed in Table 12 and summarized in Tables 13 and 14. Oral administration of chloroquine for seven days at a dose of 1.25 mg/kg cleared parasitemias but did not cure the infection in two monkeys. Doses of 2.5 and 5.0 mg/kg cured infections.

D. WR 2158AJ(BN:BL 50610), promethazine
WR 1544BM(BN:AR 20613), chloroquine

Two trials (reported previously) dealt with in vivo reversal of chloroquine-resistance by promethazine and chloroquine. In the initial trial, both drugs were administered orally at the same time, once daily, for seven days. Vietnam Smith/RE parasitemia was suppressed in 2 of 2 monkeys by 10.0 mg/kg of promethazine plus 20.0 mg/kg of chloroquine; twice the dose of promethazine plus chloroquine cleared parasitemia with recrudescence in 2 of 2 animals.

In the second trial, chloroquine (20.0 mg/kg x 7 days) was administered once daily at 8:00AM, and promethazine (10.0 or 20.0 mg/kg x 7 days) administered at 8:00AM and 4:00PM.

The parasitemia was suppressed in 1 of 2 Aotus by 10.0 mg/kg doses of promethazine plus chloroquine, while parasitemia was cleared in 1 of 2 Aotus with this dose of promethazine and in 2 of 2 Aotus by 20.0 mg/kg doses of promethazine plus chloroquine. No infections were cured by primary treatments.

Results of a third trial to reverse chloroquine-resistance in vivo are detailed in Table 15 and summarized in Tables 16 and 17. For this trial, a loading dose of chloroquine (20.0 mg/kg) was given at 8:00AM and promethazine administered at 4:00PM, for seven days. Primary treatment with promethazine (WR 2158AJ) at doses of 10.0 and 20.0 mg/kg plus chloroquine only suppressed parasitemias in a total of four Aotus. Retreatments with 20.0 mg/kg doses of promethazine to those animals originally administered 10.0 mg/kg doses, and 40.0 mg/kg doses of promethazine to monkeys originally administered 20.0 mg/kg doses, cleared parasitemias in the four monkeys. As post-treatment examination is in progress, no definitive results of retreatment are available. However, a recrudescence may occur in 12677r, having been administered 40.0 mg/kg doses of promethazine plus chloroquine.

III. Discussion

Two preparations of WR 268668 have been evaluated: a water insoluble form and a water soluble methylsulfonate salt. Evaluation results of the latter drug preparation presented in this report indicate that oral administration of the salt only suppresses parasitemias of the Vietnam Smith/RE strain. Intramuscular administration of the salt during retreatments did clear parasitemias, and although infections were cured in two monkeys, four animals died of pathogenic sequelae associated with muscle abcesses at the drug injection site.

Three newly-synthesized drugs, two trioxanes (WR 279137 and WR 279138) and a tetroxane (WR 148999) were highly active against Vietnam Smith/RE infections. Based upon this pilot evaluation, both trioxanes are as effective as arteether (WR 255131) in curing infections of a drug resistant in the Aotus model; total doses of 144.0 mg/kg of each of the three drugs cured infections. Data acquired from two animals indicate that the tetroxane is more active than arteether, as infections were cured following administration of a total dose of 96.0 mg/kg versus 144.0 mg/kg for arteether.

Blood stages of P. vivax obtained from a patient (Singleton) during a relapse after treatment with chloroquine and primaquine, and adapted to Aotus proved to be chloroquine-susceptible, as doses of 2.5 and 5.0 mg/kg (x 7 days) cured infections (2). The infection in the patient was cured when chloroquine and primaquine were given under strict supervision. Chloroquine-resistant P. vivax has yet to be reported in the New World.

The third trial to reverse chloroquine-resistance in vivo with promethazine plus chloroquine is detailed in this report. A 20.0 mg/kg loading dose of chloroquine was administered at 8:00AM, followed eight hours later with promethazine (10.0 or 20.0 mg/kg) for seven days. Primary drug administration suppressed parasitemias in 4 of 4 Aotus when compared with the untreated control infection. Retreatments at doses twice that of the primary doses cleared parasitemias in all animals. As blood film examination is in progress, no definitive statement about infection cure can be made at this time.

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TABLE 1

DETAILED ACTIVITY OF WR 268668AE(BM 11930) AGAINST INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12639	2.0a	<0.01	4	69	71	421	Re-Rx, higher dose					
12643	2.0a	<0.01	5	47	48	119	Re-Rx, higher dose					
12641	8.0a	<0.01	4	19	41	11	0.5	<0.01	<0.01	2	Re-Rx, higher dose	
12642	8.0a	<0.01	4	43	42	65	39	98	69	185	Re-Rx, higher dose	
12639r	8.0b	71	421	269	141	30	20	Re-Rx, higher dose				
12643r	8.0b	48	119	97	29	0.9	3	Re-Rx, higher dose				
12639rr	16.0b	20	6	47	54	3	0.6	<0.01	<0.01	0	0	0
12643rr	16.0b	3	0.4	7	0.2	<0.01	<0.01	<0.01	0	0	0	0
12640	32.0a	<0.01	5	33	43	2	<0.01	<0.01	<0.01	0.4	Re-Rx, higher dose	
12644	32.0a	<0.01	5	53	13	1	<0.01	<0.01	<0.01	<0.01	<0.01	0.9 Re-Rx
12641r	32.0b	2	87	39	3	0.2	0.4	1	<0.01	<0.01	<0.01	<0.01
12642r	32.0b	69	185	99	2	0.4	<0.01	<0.01	<0.01	<0.01	0.7	Re-Rx
12640r	64.0b	0.4	11	1	0.4	<0.01	0	0	0	0	0	0
12644r	64.0b	0.9	0.9	<0.01	0	Died, drug toxicity						
12642rr	64.0a	0.7	1	<0.01	0	0	0	0	0	0	0	0

a Oral administration
b Intramuscular administration

TABLE 2

SUMMARY OF THE ACTIVITY OF WR 268668AE (BM 11930) AGAINST INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Daily Dose x 3 Mg/kg	Response of Parasitemia to Rx			Days from Initial Rx to parasite Clearance	Days from Final Rx To Recru-descence	Notes No. of days negative
		None	Suppressed	Cleared			
12639	2.0a		±		n.a.	n.a.	Re-Rx, higher dose
12643	2.0a		±		n.a.	n.a.	Re-Rx, higher dose
12641	8.0a		+		n.a.	n.a.	Re-Rx, higher dose
12642	8.0a		+		n.a.	n.a.	Re-Rx, higher dose
12639r	8.0b		+		n.a.	n.a.	Re-Rx, higher dose
12643r	8.0b		+		n.a.	n.a.	Re-Rx, higher dose
12639rr	16.0b			+	8	n.a.	Cured
12643rr	16.0b			+	7	n.a.	Cured
12640	32.0a		+		n.a.	n.a.	Re-Rx, higher dose
12644	32.0a		+		n.a.	n.a.	Re-Rx, higher dose
12641r	32.0b			+	12	n.a.	Died, day 35 post Rx, toxicity
12642r	32.0b		+		n.a.	n.a.	Re-Rx, higher dose
12640r	64.0b			+	5	n.a.	Died day 19 post Rx, toxicity
12644r	64.0b				n.a.	n.a.	Died day 1 Post-Rx, toxicity(?)
12642rr	64.0a			+	3	n.a.	Died day 25 post Rx, toxicity

a = oral

b = intramuscular

TABLE 3

SUMMARY OF THE ACTIVITY OF WR 268668AE(BM 11930) AGAINST *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
Smith/RE	6.0	3.0	0/2	0/2			0/2	0/2
	24.0a	8.0	0/2	0/2			0/2	0/2
	24.0b	8.0	0/2	0/2			0/2	0/2
	48.0b	16.0			2/2	2/2	2/2	2/2
	96.0a	32.0	0/2	0/2			0/2	0/2
	96.0b	32.0			1/2	0/1	1/2	0/1
	192.0a	64.0			1/1	0/1	1/1	0/1
	192.0b	64.0			1/1	0/1	1/1	0/1

TABLE 4

TOXICITY EVALUATION OF WR 148999AC(BM 11681)

Monkey No.	Drug mg/kg	Body Weight (gms) Days Post Treatment					
		-2	7	14	31	38	48
11334	144.0	769	785	801	776	777	769

Drug administered intramuscularly, Day 1 at 8:00 AM and 8:00 PM, Day 2 - 8:00 AM

TABLE 5

DETAILED ACTIVITY OF WR 279137AA(BM 12115) AGAINST INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Rx		Day Post Treatment							
			1	2	1	2	3	4	5	6	7	8
12665	12.0	10	14	72	19	<0.01	<0.01	0	0	0	0	0
12666	12.0	13	44	97	28	<0.01	<0.01	0	0	0	0	0
12659	48.0	1	1	14	0.6	<0.01	<0.01	0	0	0	0	0
12660	48.0	18	50	129	9	<0.01	<0.01	0	0	0	0	0
12666r	48.0	12	47	5	<0.01	<0.01	0	0	0	0	0	0
12647	48.0a)	13	9	2	0.8	<0.01	<0.01	<0.01	<0.01+	<0.01+	<0.01+	0
12648	48.0a)	20	23	1	0.2	<0.01	<0.01	<0.01	<0.01+	<0.01+	0	0

Drugs administered intramuscularly, 3 doses, 8:AM, 8:00PM, 8:00AM

a WR 255131AE(BL 48816), arteether

+ Drug forms

TABLE 6

SUMMARY OF THE ACTIVITY OF WR 279137AA(BM 12115) AGAINST INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Dose x 3 Mg/kg	Response of Parasitemia to Rx			Days from Initial Rx to parasite Clearance	Days from Final Rx To Recru-descence	Notes No. of days negative
		None	Suppressed	Cleared			
12665	12.0			+	6	n.a.	Cured
12666	12.0			+	6	21	Re-Rx, higher dose
12659	48.0			+	6	n.a.	Cured
12663	48.0			+	6	n.a.	Cured
12666r	48.0			+	5	n.a.	Cured
12647	48.0*			+	10	n.a.	Cured
12648	48.0*			+	9	n.a.	Cured

Drugs administered intramuscularly, 3 doses, 8:00AM, 8:00PM, 8:00AM

* WR 255131AE(BL 48816), arteether

TABLE 7

DETAILED ACTIVITY OF WR 279138AA(BM 12124) AGAINST INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Rx		Day Post Treatment							
			1	2	1	2	3	4	5	6	7	8
12661	12.0	32	32	164	144	Re-Rx, higher dose						
12662	12.0	14	33	62	134	Re-Rx, higher dose						
12653	48.0	14	24	95	20	0.5	<0.01	0	0	0	0	0
12656	48.0	24	88	273	60	0.3	<0.01	0	0	0	0	0
12661r	48.0	144	0.9	0.6	<0.01	<0.01	0	0	0	0	0	0
12662r	48.0	134	0.1	<0.01	<0.01	0	0	0	0	0	0	0
12647	48.0a	13	9	2	0.8	<0.01	<0.01	<0.01	<0.01+	<0.01+	<0.01+	0
12648	48.0a	20	23	1	0.2	<0.01	<0.01	<0.01	<0.01+	<0.01+	0	0

Drugs administered intramuscularly, 3 doses, 8:00 AM, 8:00PM, 8:00AM

a WR 255131AE(BL 48816), arteether

+ Drug forms

TABLE 8

SUMMARY OF THE ACTIVITY OF WR 279138AA(BM 12124) AGAINST INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Dose x 3 Mg/kg	Response of Parasitemia to Rx			Days from Initial Rx to parasite Clearance	Days from Final Rx To Recru-descence	Notes No. of days negative
		None	Suppressed	Cleared			
12661	12.0		+		n.a.	n.a.	Re-Rx, higher dose
12662	12.0		+		n.a.	n.a.	Re-Rx, higher dose
12653	48.0			+	6	n.a.	Cured
12656	48.0			+	6	n.a.	Cured
12661r	48.0			+	5	n.a.	Cured
12662r	48.0			+	4	n.a.	Cured
12647	48.0*			+	10	n.a.	Cured
12648	48.0*			+	9	n.a.	Cured

Drugs administered intramuscularly, 3 doses, 8:00AM, 8:00PM, 8:00AM

* WR 255131AE(BL 48816), arteether

TABLE 9

DETAILED ACTIVITY OF WR 148999AC(BM 11681) AGAINST INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Rx		Day Post Treatment							
			1	2	1	2	3	4	5	6	7	8
12651	32.0	8	11	50	0.5	<0.01	0	0	0	0	0	0
12652	32.0	5	15	42	0.5	<0.01	<0.01	<0.01	0	0	0	0
12645	144.0	17	29	72	8	<0.01	<0.01	0	0	0	0	0
12646	144.0	32	23	55	3	<0.01	<0.01	0	0	0	0	0
12647	48.0a	13	9	2	0.8	<0.01	<0.01	<0.01	<0.01+	<0.01+	<0.01+	0
12648	48.0a	20	23	1	0.2	<0.01	<0.01	<0.01	<0.01+	<0.01+	0	0

Drugs administered intramuscularly, 3 doses, 8:00 AM, 8:00 PM, 8:00 AM

a WR 255131AE(BL 48816), arteether

\+ Drug forms

TABLE 10

SUMMARY OF THE ACTIVITY OF WR 148999AC(BM 11681) AGAINST

INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Dose x 3 Mg/kg	Response of Parasitemia to Rx			Days from Initial Rx to parasite Clearance	Days from Final Rx To Recru-descence	Notes No. of days negative
		None	Suppressed	Cleared			
12651	32.0			+	5	n.a.	Cured
12652	32.0			+	7	n.a.	Cured
12645	144.0			+	6	n.a.	Neg. 79 days, **
12646	144.0			+	6	n.a.	Cured
12647	48.0*			+	10	n.a.	Cured
12648	48.0*			+	9	n.a.	Cured

Drugs administered intramuscularly, 3 doses, 8:00AM, 8:00PM, 8:00AM

* WR 255131AE(BL 48816), arteether

** Escaped from animal quarters

TABLE 11

SUMMARY OF THE ACTIVITIES OF TRIOXANES AND TETROXANE AGAINST 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
Smith/RE								
			WR 279137AA(BM 12115)					
	36.0	12.0	2/2	1/2			2/2	1/2
	144.0	48.0	2/2	2/2	1/1	1/1	3/3	3/3
			WR 279138AA(BM 12124)					
	36.0	12.0	0/2	0/2			0/2	0/2
	144.0	48.0	2/2	2/2	2/2	2/2	4/4	4/4
			WR 148999AC(BM 11681)					
	96.0	32.0	2/2	2/2			2/2	2/2
	432.0	144.0	2/2	1/2			2/2	1/2
			WR 255131AE(BL 48816)					
	144.0	48.0	2/2	2/2			2/2	2/2

TABLE 12

DETAILED ACTIVITY OF WR 1544BM(AR 20613) AGAINST INFECTIONS OF THE SINGLETON STRAIN OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3									
		Day Pre-Rx	Day of Treatment							Day Post Treatment		
			1	2	3	4	5	6	7	1	2	3
11610	1.25	1	2	6	3	2	0.5	0.2	0.04	<0.01	0	0
11896	1.25	1	4	12	22	18	2	3	0.4	<0.01	0	0
11093	2.5	1	2	3	0.9	<0.01	0	0	0	0	0	0
11926	2.5	1	2	0.3	<0.01	0	0	0	0	0	0	0
11869	5.0	1	2	0.1	<0.01	0	0	0	0	0	0	0
11980	5.0	2	5	1	<0.01	<0.01	0	0	0	0	0	0

TABLE 13

SUMMARY OF THE ACTIVITY OF WR 1544BM(AR 20613) AGAINST INFECTIONS OF THE SINGLETON STRAIN OF PLASMODIUM VIVAX

Monkey No.	Dose x 7 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recrudescence	Notes
		None	Suppressed	Cleared			
11610	1.25			+	9	14	
11896	1.25			+	9	9	
11093	2.5			+	5	n.a.	Cured
11926	2.5			+	4	n.a.	Cured
11869	5.0			+	4	n.a.	Cured
11980	5.0			+	5	n.a.	Cured

TABLE 14

SUMMARY OF THE ACTIVITY OF WR 1544BM (AR 20613) AGAINST 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
Singleton	8.75	1.25	2/2	0/2			2/2	0/2
	17.5	2.5	2/2	2/2			2/2	2/2
	35.0	5.0	2/2	2/2			2/2	2/2

TABLE 15

DETAILED ACTIVITY OF WR 2158AJ(BL 50610) AND WR 1544BM (AR 20613) AGAINST INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3									
		Day Pre-Rx	Day of Treatment							Day Post Treatment		
			1	2	3	4	5	6	7	1	2	3
12678	10.0a 20.0b	21	159	489	180	162	14	7	0.3	0.1	0.3	0.2
12680	10.0a 20.0b	25	202	296	236	139	149	110	59	3	3	2
12677	20.0a 20.0b	19	168	271	142	129	15	9	0.6	0.08	0.06	<0.01
12679	20.0a 20.0b	19	125	158	138	74	21	10	0.2	0.05	<0.01	<0.01
12678r	20.0a 20.0b	5	4	4	2	0.1	<0.01	<0.01	0	0	0	0
12680r	20.0a 20.0b	88	91	59	8	0.1	0.1	<0.01	0	0	0	0
12677r	40.0a 20.0b	0.7	1	2	0.2	<0.01	0	0	0	0	0	<0.01
12679r	40.0a 20.0b	<0.01	<0.01	<0.01	0.2	0.3	0.3	<0.01	0	0	0	0

a WR 2158AJ, promethazine, Rx 4:00PM
b WR 1544BM, chloroquine, Rx 8:00AM

TABLE 16

SUMMARY OF THE ACTIVITY OF WR 2158AJ(BL 50610) AND WR 1544BM (AR 20613) AGAINST INFECTIONS OF THE VIETNAM SMITH/RE STRAIN OF *PLASMODIUM FALCIPARUM*

Monkey No.	Dose x 7 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
12678	10.0a 20.0b		+		n.a.	n.a.	Re-Rx, higher dose
12680	10.0a 20.0b		+		n.a.	n.a.	Re-Rx, higher dose
12677	20.0a 20.0b		+		n.a.	n.a.	Re-Rx, higher dose
12679	20.0a 20.0b		+		n.a.	n.a.	Re-Rx, higher dose
12678r	20.0a 20.0b			+	7		Neg. 4 days, In progress
12680r	20.0a 20.0b			+	7		Neg. 4 days, In progress
12677r	40.0a 20.0b			+	5	3?	In progress
12679r	40.0a 20.0b			+	7		Neg. 4 days, In progress

a WR 2158, promethazine, Rx 4:00PM
b WR 1544, chloroquine, Rx 8:00AM

TABLE 17

SUMMARY OF TRIALS TO REVERSE CHLOROQUINE-RESISTANCE OF 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
Smith/RE								
			WR 2158AJ (a) plus WR 1544BM (b)					
	70.0a 140.0b	10.0 20.0	0/2	0/2			0/2	0/2
	140.0a 140.0b	20.0 20.0	0/2	0/2	2/2	?/2	2/4	In progress
	280.0a 140.0b	40.0 20.0			2/2	?/2		In progress

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 7 Feb 97

MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-OCP, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for Contract Number DAMD17-91-C-1072. Request the limited distribution statement for Accession Document Numbers ADB214740, ADB198405, ADB210896, ADB183789, and ADB173254 be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Mrs. Judy Pawlus at DSN 343-7322.

FOR THE COMMANDER:

GARY R. GILBERT
Colonel, MS
Deputy Chief of Staff for
Information Management

Completed
22 May 2000
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