

Evaluation of WR 33063 in the Treatment of Acute Falciparum Malaria

Principal Investigator : Herbert E. Segal, MAJ, MC

Associate Investigators : Prem Chinvanthananond, M.D.*
Bunharn Laixuthai, LTC, MC, RTA
Pung Phintuyothin, MG, RTA (ret.)
Eliot J. Pearlman, MAJ, MC
Ben F. Castaneda, SFC

OBJECTIVE: To study the therapeutic efficacy of an investigational phenanthrenemethanol antimalarial, WR 33063.

DESCRIPTION: This study was carried out at the Prachinburi Provincial Hospital, in Northeast Thailand, during a four-month period in mid-1972. Male patients presenting with acute, uncomplicated falciparum malaria with between 1,000 and 100,000 asexual parasites per cubic millimeter of blood were selected for study and hospitalized six days. Subjects were randomly assigned to either the "Study Group" or the "Control Group". The "Study Group" received WR 33063, 600 milligrams every eight hours for six days. The control group was treated with quinine sulfate, 625 milligrams every eight hours for six days. Twice daily during hospitalization each subject was examined and capillary blood taken for quantitative parasite counts. Subjects were followed after discharge and capillary blood was collected for quantitative parasite counts on days 14, 21 and 28.

PROGRESS: Fifty-one patients met the criteria for admission and were treated, 25 with WR 33063 (Study Group) and 26 with quinine sulfate (Control Group). The mean ages for the Study and Control Group were 28.1 and 25.5 years and the mean admission asexual parasite counts 29,492 and 25,272 parasites per cubic millimeter of blood respectively. All patients admitted to the study completed the specified period of hospitalization. The mean asexual parasite clearance time for the Study Group was 66.4 hours, compared with 65.1 hours for the Control Group ($t=0.21$, $0.90 > p > 0.80$). The mean fever defervescence times were 58.5 and 59.7 hours for the Study and Control Groups, respectively ($t=0.12$, $0.95 > p > 0.90$).

Symptoms of fever, insomnia, nausea and vomiting, abdominal pain, constipation, and myalgia were expressed slightly more often by Study Group subjects. Control Group subjects complained of headache slightly more often, and of tinnitus, blurred vision, chest pain, and diarrhea much more commonly. Complaints of dizziness and anorexia were equally distributed in both groups. Complaints voiced during the day of admission were not included (Table 1). Several subjects had biochemical evidence of hepatic dysfunction on admission. In no subject in the Study or Control Groups did serum bilirubin, alkaline phosphatase, creatinine, or transaminase values either become abnormal during therapy or rise to levels greatly in excess of admission values (Table 2).

Twenty-two of 25 Study Group subjects (88%) completed the follow-up period. The three who did not were re-treated for vivax malaria on day 21 (two subjects) and day 23 (one subject). All had been falciparum negative by smear to that time. Of the 22 subjects completing follow-up, 20 (90%) remained smear negative through day 28 and were considered cured. Of the two patients not cured, one infection was unresponsive (R3 pattern) and was successfully treated with intravenous followed by oral quinine. The other subject was not parasitemic until the day 28 follow-up (R1) and was admitted to a later SMRL study.

* Chao Phya Abhai Bhu Bejhr Hospital, Prachinburi

Twenty-one of the 26 Control Group subjects (81%) completed follow-up. One of those who did not was re-treated for vivax malaria (day 20); four others changed their residence and were lost at day 17 (one subject), at day 21 (one subject), and at day 28 (two subjects). All five had remained falciparum negative until their loss to the study. Of subjects completing follow-up, 20 (95%) were cured. The single infection not cured responded partially (R2 pattern); this patient was re-treated with chloroquine-primaquine but did not return for follow-up.

The circumstances of follow-up do not exclude the possibility of reinfection. It is possible that the falciparum parasitemia found in one Study Group subject on day 28 represents a new infection. A more likely explanation for the vivax parasitemias found is that they represent relapsing infections suppressed by drug treatment.

SUMMARY: The investigational drug employed in this study appears comparable in its therapeutic efficacy to quinine sulfate and somewhat better tolerated by the study subjects.

Table 1.
Reported Symptoms, WR 33063 and
Quinine Sulfate—Treated Patients

Symptom	WR 33063 (25 Patients)	Quinine Sulfate (26 Patients)
Headache	8	11
Fever	6	5
Dizziness	2	2
Tinnitus	4	12
Insomnia	4	2
Blurred Vision	0	3
Chest Pain	0	2
Anorexia	4	4
Nausea, Vomiting	3	2
Abdominal Pain	4	2
Diarrhea	1	4
Constipation	1	0
Myalgia	2	0

Table 2.
 Biochemical Studies, WR 33063 — and
 Quinine Sulfate—Treated Patients

Serum Specimens	Mean (Range) Serum Values					
	Bilirubin ¹		Alkaline Phosphatase ²	Creatinine ³	SGOT ⁴	
	Direct	Total				
WR 33063						
day 0	0.56 (0.1—3.0)	1.29 (0.3—3.8)	2.53 (0.8—6.1)	1.30 (0.6—6.5)	39.1 (15—97)	
day 3	0.44 (0.0—1.2)	0.78 (0.1—1.7)	2.46 (1.1—5.1)	1.18 (0.6—8.5)	30.2 (11—72)	
day 6	0.32 (0.0—0.9)	0.78 (0.1—1.2)	2.38 (1.1—4.7)	0.96 (0.5—5.5)	31.9 (11—106)	
day 28	0.25 (0.0—0.9)	0.57 (0.1—1.5)	2.87 (1.3—7.0)	0.79 (0.5—1.3)	26.1 (13—59)	
QUININE						
day 0	0.69 (0.1—5.1)	1.34 (0.3—6.1)	2.07 (1.0—4.7)	1.39 (0.5—6.8)	29.1 (14—75)	
day 3	0.64 (0.1—4.2)	0.91 (0.2—4.9)	1.90 (0.8—4.2)	1.22 (0.5—5.3)	24.9 (3—38)	
day 6	0.46 (0.0—3.4)	0.68 (0.1—3.7)	1.86 (0.9—3.9)	1.04 (0.6—3.2)	23.8 (14—55)	
day 28	0.23 (0.0—0.6)	0.50 (0.1—1.1)	2.53 (1.4—5.7)	0.78 (0.5—1.2)	25.9 (17—41)	

¹ Milligrams percent

² Sigma units

³ Milligrams percent

⁴ Sigma—Frankel units