

Comparison of a 9-Phenanthrene Methanol (WR33063), a 4-Quinoline Methanol (WR30090), and Quinine for Treatment of Falciparum Malaria in Thailand

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**OBJECTIVE:** To compare the efficacy of WR33063, WR30090, and quinine against falciparum malaria in Thailand.

**BACKGROUND:** WR33063 and WR30090 are the code numbers for 2 antimalarial drugs developed by the U.S. Army Malaria Research Program.

WR33063 is a 9-phenanthrene methanol which in volunteers did not cause toxicity up to 4.6 grams daily for 10 days; and 1.6 grams daily for 6 days was highly effective against all the strains of *P. falciparum* that were tested.<sup>(1)</sup>

WR30090 is a 4-quinoline methanol which was non-toxic in volunteers who received 0.69 grams daily for 6 days. At this dose the drug radically cured all chloroquine-sensitive and most chloroquine resistant infections with *P. falciparum*.<sup>(2)</sup>

Canfield et al<sup>(3)</sup> tested both drugs in U.S. soldiers with acute falciparum malaria in Vietnam. The radical cure rate for WR33063 was 92% (23/25) and for WR30090 was 88% (23/26). Other patients with recrudescing infections were all cured by one or the other of these new drugs. Segal et al<sup>(4)</sup> studied indigenous patients in Northeast Thailand and found a cure rate of 92% (23/25) for WR33063 and of 94% (24/25) for quinine.

The present study extends the comparison of WR33063, WR30090 and quinine to Southeast Thailand, another area of known multi-drug parasite resistance.

**DESCRIPTION:** Colwell et al<sup>(5)</sup> reported on the first of several malaria studies sponsored jointly by the SEATO Medical Research Laboratory and the Trad Provincial Hospital in Southeast Thailand 400 km from Bangkok. Malaria is transmitted continuously throughout the year in Trad Province.

The present studies were begun on 11 January 1973. Patients reporting to the hospital with suspected malaria were referred to a special malaria clinic. Blood was obtained from a finger prick and a thin film, a circular thick film, and a measured 3×15 mm rectangular thick film containing 0.002 ml blood were made. The slides were stained with Giemsa at 1:5 dilution for 5 minutes. If examination of the blood films showed plasmodia, a direct parasite count was done on the measured film using the method of Earle and Perez<sup>(6)</sup> as described by Powell et al.<sup>(7)</sup>

On patients admitted to a therapeutic study, the second and all subsequent slides, which included 2 rectangular films each using 0.05 ml blood, were stained with Giemsa at 1:50 dilution for 30 minutes. Parasite counts were performed twice daily on capillary blood specimens taken at 0700 and 1400 hours from day 0 to day 6, or until two negative blood films were obtained; thereafter, specimens were obtained

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once daily. Parasite counts were performed at other times when indicated. Follow-up smears were made on days 14, 21 and 28.

Determinations of hematocrit levels and leucocyte counts were made on admission and on days 3, 6 and 28. Sera were collected on days 0, 3, 6 and 28, and whenever the clinical response was unusual, for measurements of creatinine, glutamic-oxaloacetic transaminase (SGOT), bilirubin and alkaline phosphatase. Urinalysis was performed on admission and on days 3, 6 and 28.

From the patients with falciparum malaria who required treatment in hospital, volunteers were selected for the study who met the following criteria :

1. Males at least 15 years old who agreed to the use of the drugs which were under investigation and who were willing to be in hospital for 6 days and to attend 3 follow-up visits on days 14, 21 and 28 (the day of admission being called day 0).
2. Asexual parasite counts of *P. falciparum* between 1,000 and 100,000 per cmm.
3. Evidence of active disease as shown by a rising parasite count, a high fever, or obvious symptoms (e.g. headache).

Patients with severe or complicated falciparum malaria were not studied nor were those with coincident vivax malaria.

The patients were attended by the SEATO physicians throughout the study, under the supervision of the Trad Medical staff. The nurses took oral temperatures routinely at 0600 and 1800. Additional readings were taken during febrile episodes. Ward rounds were made at least twice daily and at other times when clinically indicated. Palpation for splenomegaly was done at least once daily.

On the day of discharge (day 6 or later) the patients were handed a follow-up card and then taken home in a truck by the SEATO driver who drew a map of the route on returning to the clinic. If the patients failed to attend the follow-up clinic on days 14, 21 and 28, home visits were made.

A table of random numbers was used to assign the patients to one of the following drugs :

- a. WR33063 was formulated in yellow and green gelatin capsules containing 200 mg of the drug. The dose was 600 mg (3 capsules) every 8 hours for 18 doses (6 days). The total dose was 10.8 grams.
- b. WR30090 was formulated in red and white gelatin capsules containing 250 mg of the drug. The dose was 250 mg (1 capsule) every 8 hours for a total of 18 doses (6 days). The total dose was 4.5 grams.
- c. The quinine was administered in brown sugar-coated tablets of quinine sulfate, USP, each containing 270 mg quinine base. The dose was 540 mg (2 tablets) every 8 hours for 18 doses (6 days). The total dose was 9.72 grams.

Throughout the study, the drugs were administered by the technicians or the doctors. We evolved a team concept whereby the doctor and the technician combined the ward rounds and medication administration at 0600, 1400 and 2200 hrs. The drug for each patient was kept in a bottle labelled with the patient's name, study number and bed number. The number of capsules or tablets in each bottle was double checked before treatment. The "Medication Ward Round" was conducted in the following sequence :

1. With the technician as interpreter, the patient was asked how he felt. Evidence of drug toxicity would result in a reduced or deleted dose.
2. The patient swallowed the drug followed by water.

3. The spleen was palpated while the patient breathed through his mouth. We could thus detect whether the drug had been swallowed or retained in the mouth.

4. The symptoms and signs were noted and the doctor recorded each dose on individual sheets for each patient.

5. The patients were then asked to stay in bed for 30 minutes and were observed by the study team during this period.

*PROGRESS:* Between January and August 1973, blood films were examined on 4213 people of whom 1705 had falciparum malaria (including a few mixed infections) and 284 had vivax malaria.

214 patients were admitted to the therapeutic study between 11 January and 2 August 1973. 207 of these patients completed the 6 day treatment in hospital.

The similarity of the study groups is shown in Table 1. The average age was 27 years. There was no difference in the mean temperature or parasite count. WR 33063 cleared parasitemia slower than quinine (77 vs 70 hours) but temperatures returned to normal more rapidly with WR 33063 than with the other 2 drugs. The differences were not statistically significant.

In 204 patients the parasitemia was cleared during the hospital course. In the 3 other patients the parasitemia was not cleared by the initial therapy.

The 3 drugs caused no detectable changes in hematocrit, WBC count, creatinine, SGOT, bilirubin, alkaline phosphatase or urinalysis.

One patient (case No. 216) had heavy proteinuria (2.3 grams per cent) and a serum albumin of 1.13 grams per cent on the day of admission before therapy with WR 33063. During treatment he developed gross pitting edema of the abdomen and legs and the heavy proteinuria continued. The malaria was cured but the nephrotic syndrome persisted despite corticosteroid therapy.

Complete follow-up was achieved in 190 of the 207 patients who were admitted to the study (92%). Follow-up was 100% for local residents but only 63% (29/46) for patients who had recently migrated from other parts of Thailand.

21 patients developed a repeat attack, on or before day 28, diagnosed as a recrudescence. 12 patients had a repeat attack, between day 29 and day 147, diagnosed as a reinfection. This arbitrary classification followed established practice.

Patients whose infections were cleared and did not recur on or before day 28 were considered to be cured. The cure rates for the 3 study drugs compared with 5 other drugs we have studied is shown in Table 2. Chloroquine and pyrimethamine resistance were confirmed. WR 33063 had the highest cure rate, although the differences between the 3 study drugs were not statistically significant.

Patients who were not cured had significantly higher initial parasite counts and more prolonged parasitemia and fever (Table 3). This group includes 3 patients with an RII or RIII response and 21 with an RI response. Patients with repeat attacks after day 28 (i.e. diagnosed as reinfections) responded, as a rule, like patients in the "cured" group. This suggests that day 28 is a reasonable dividing line between recrudescence and reinfection.

20% (37/190) of the followed-up patients developed an attack of vivax malaria before day 29. All attacks responded to chloroquine.

WR 33063 was the least toxic drug and caused no specific side effects. In no patient did drug administration have to be stopped or the dose reduced.

Table 1. Comparison of WR 33063, WR 30090 and Quinine Initial Response

Drug	No. Patients	Mean Asexual Parasite Count (per cmm)	Mean* Parasite Clearance (Hours)	Mean** Highest Temperature (°C)	Mean*** Fever Clearance (Hours)
WR 33063	69	27,894	77.2 ± 2.6 (68)	39.2	54.5 ± 3.8 (56)
WR 30090	68	27,520	71.6 ± 2.7 (65)	39.4	58.4 ± 3.7 (61)
Quinine	70	27,745	69.8 ± 2.5 (69)	39.0	63.7 ± 4.5 (57)

\* Mean ± Standard Error of Mean. The figures in parentheses refer to the number of patients observed.

\*\* Highest temperature on day of admission.

\*\*\* Fever clearance times computed only if initial fever > 38.0°C.

Table 2. Treatment of Falciparum Malaria in Southeast Thailand 1973

Drug*	Mean parasite Count Per cmm	R III**				Total	Cure Rate	No. Doses In Regimen
		R III	R II	R I	S			
WR 33063	27,000	1	0	4	57	62	92%	18
WR 30090	28,000	0	1	8	54	63	86%	18
Quinine	28,000	1	0	9	55	65	85%	18
Fansidar***	28,000	0	2	1	14	17	82%	1
Amodiaquine	20,000	0	2	6	5	13	38%	4
Maloprim***	24,000	0	0	17	4	21	19%	1
Chloroquine	15,000	2	8	1	0	11	0%	4
Pyrimethamine	3,000	0	3	0	0	3	0%	3

\* Dosage

WR33063: 600 mg T.I.D. 6 days

WR30090: 250 mg T.I.D. 6 days

Quinine: 540 mg (base) T.I.D. 6 days

Fansidar: Sulformethoxine 1.0 g. } 1 dose  
Pyrimethamine 50 mg }

Maloprim: DDS 200 mg } 1 dose  
Pyrimethamine 25 mg }

Amodiaquine: 1.5 g in 3 days

Chloroquine: 1.5 g in 3 days

Pyrimethamine: 150 mg in 3 days

\*\* R III, no marked reduction of asexual parasitemia; R II, marked reduction of asexual parasitemia but no clearance; R I, clearance, followed by recrudescence; S, Clearance without recrudescence. World Health Organization (1967) Chemotherapy of malaria. WHO Tech Rep Ser No. 375, p 42.

\*\*\* Study performed in Northeast Thailand by Segal et al (1974 b)

Table 3. WR 30090, WR 33063, Quinine. Comparison of Patients Cured and Not Cured

Characteristic	Cured (S)	Not Cured (RI-III)	Statistical Significance
Number of Patients	183	24	
Mean Initial Parasite Count (per cmm)	25,600	43,900	$t = 2.7, p < 0.02$
Mean Parasite Clearance (Hours)	71	88	$t = 2.9, p < 0.01$
Mean Initial Fever ( $^{\circ}\text{C}$ )	39.2	39.2	$t = 0, \text{Not Significant}$
Mean Fever Clearance (Hours)	56	79	$t = 3.2, p < 0.01$

Headache and backache were more common in the patients receiving WR 30090. Urticaria, probably due to WR 30090, occurred in two patients.

Quinine caused cinchonism in many patients and was the most toxic drug. Many patients were seen lying down at unusual times, presumably because of postural hypotension. The dose of quinine had to be reduced in 15 patients (20%) because of severe toxicity.

Drug fever was tentatively diagnosed in 9 patients on quinine, 3 patients on WR 30090, and 1 patient on WR 33063.

All 3 drugs were inconvenient to use because they had to be administered every 8 hours for 6 days. Most patients were otherwise fit for discharge on the third day, so that the treatments caused delay in discharge and overflow of the wards. Convenient therapy should be finished within 3 days, and, if possible, be comprised of only 1 or 2 doses daily.

*DISCUSSION:* WR33063 was a highly effective drug. In comparison with WR30090 and quinine, WR33063 had the highest cure rate, cleared fever the most rapidly and had the lowest toxicity. WR33063, however, was slower than quinine in clearing parasitemia. The main disadvantage of WR33063 was its bulky formulation (3 capsules for each dose).

WR30090 was also as effective as quinine, especially in clearing parasitemia. This drug appeared to cause headache, backache and urticaria but was not as toxic as quinine. In contrast, WR30090 showed no toxicity in the more limited number of cases reported by Martin et al<sup>(2)</sup> and Canfield et al<sup>(3)</sup>.

Altogether, WR33063 appears to be the more promising of the 2 new drugs.

In this study, patients with a prolonged parasitemia or a prolonged fever were more liable to develop recrudescences. Similar results were obtained in U.S. troops by Hall<sup>(8)</sup>. Thus, these 2 parameters (parasite clearance time and fever clearance time) may be a useful guide in evaluating the radical curative potential of an antimalarial drug.

We have observed that intravenous quinine is more effective than oral quinine in bringing a malarial attack under control; therefore, it is wise to use oral quinine alone against mild infections only, and to precede oral therapy with intravenous quinine for more severe infections.

20% of the patients developed attacks of vivax malaria during the follow-up period and these caused many days lost from work. Routine administration of primaquine after discharge (e.g., 15 mg daily for up to 14 days) may be the answer.

In patient No. 216 the nephrotic syndrome was probably caused by the falciparum malaria. Such an entity has been proposed by Berger et al<sup>(9)</sup>.

**SUMMARY:** Quinine was compared with a 9-phenanthrene methanol (WR 33063) and a 4-quinoline methanol (WR 30090) in the treatment of 207 patients with falciparum malaria in Southeast Thailand. Quinine eradicated parasitemia (average 70 hours) more rapidly than either WR 30090 (72 hours) or WR 33063 (77 hours); but WR 33063 had a higher cure rate (92%) than WR 30090 (86%) or quinine (85%).

WR 33063 was the least toxic drug. WR 30090 appeared to cause headache, backache and urticaria. Quinine was the most toxic drug. All 3 drugs were inconvenient in having to be administered every 8 hours for 6 days. One patient did not respond to oral quinine but did respond to an intravenous quinine infusion.

A "Medication Ward Round" was perfected during the study and comprised sequential history, drug administration, physical examination, dose notation and patient observation. Falciparum nephrosis was diagnosed in one patient.

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