

Malaria—Clinical Studies and Observations

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BACKGROUND: As a result of the major efforts in antimalarial drug testing reported elsewhere, we have been afforded a unique opportunity to observe and manage large numbers of patients with malaria attending Trad Provincial Hospital. This report documents observations made upon groups of patients from this population.

Treatment of Falciparum Malaria with Septrin: Septrin, a 5:1 combination of sulfamethoxazole and trimethoprim is commonly used in the treatment of bacterial infections. It has been moderately successful in antimalarial therapy. Three patients with *P. falciparum* infections were given Septrin. Results are summarized in Table 1.

Table 1. Falciparum Malaria Treated with Septrin

Case Number	Parasite Count (per cmm)	Parasite Clearance (Hours)	Initial Fever (°C)	Fever Clearance (Hours)	Comment
1	7280	51	39.0	44	
2	46980	51	38.6	20	
3	49248	48	37.5	—	Quinine Therapy added

In cases 1 and 2 a satisfactory clinical response occurred in hospital. In case 3, it was decided on the day of admission that, because of the patient's symptoms, quinine therapy was also indicated. Follow-up studies on these patients have not yet been completed.

Treatment of Falciparum Malaria with Proguanil: Proguanil, probably the least toxic antimalarial, was introduced in 1945. By 1950 falciparum malaria resistant to proguanil had been encountered and the drug fell into disfavor. Nonetheless, the Australian Army in Vietnam utilized proguanil with DDS, daily, as prophylaxis with apparent success.

One patient with *P. falciparum* infection at Trad Hospital was treated with proguanil. The patient was a 49 year old man with clinically mild disease. The parasite count was 48,924 per cmm, and oral temperature 38.2°C. Proguanil 200 mg was given as a loading dose then 100 mg was given twice daily for a total of 12 doses. His fever responded slowly (clearance time 115 hours), as did his parasitemia (clearance time 98 hours). Follow-up has not been completed.

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In the patient studied, proguanil, like many other partially effective drugs (e.g. Fansidar, Septrin, Amodiaquine), was slow to bring the clinical symptoms under control. These partially effective drugs should not be used for the primary treatment of the disease. Quinine is the drug of choice, although it is often toxic, and falciparum malaria in Thailand often shows partial resistance. Further studies with proguanil will be conducted.

Quinine Fever in Falciparum Malaria: In a recently completed study, quinine was compared with 2 investigational drugs (WR30090 and WR33063). Each of the 3 drugs was given to malaria patients for 6 days. The temperature charts and clinical histories were reviewed for evidence of drug-induced fever.

The criteria for the diagnosis of quinine fever (QF) were a fever which persisted or developed after parasitemia had been cleared, and the absence of evidence of another disease. All cases in which the fever clearance time exceeded the parasite clearance time by at least 12 hours were reviewed.

The study involved 207 patients. The mean fever clearance times for WR33063, WR30090 and quinine were 55, 58 and 64 hours respectively; and the mean parasitemia clearance times were 77, 72 and 70 hours. Thus the differences between mean parasite clearance times and mean fever clearance times were 22, 14 and 6 hours for WR33063, WR30090 and quinine respectively. The magnitude of these differences appears to inversely reflect the potential of the drugs to cause a fever, i.e., quinine was much more likely than WR33063 to produce a drug fever. QF was diagnosed in 10% (9/70) of the patients treated; WR 30090 fever in 4% (3/68); and WR33063 fever in 1% (1/69). Details of the 9 QF patients are shown in Table 2; on average the fever clearance time exceeded the parasite clearance time by 40 hours.

Quinine fever is one, but certainly not the most serious, manifestation of quinine toxicity.

Table 2. Quinine Fever in Thailand

Case Number	Initial Fever (°C)	Parasite Clearance Time (Hours)	Fever Clearance Time (Hours)	Difference FCT—PCT (Hours)	Peak Fever During QF (°C)*
24	40.3	46	114		39.5
45	40.7	76	96	20	39.3
54	39.7	93	107	14	38.3
99	38.2	58	104	46	39.0
120	39.5	69	133	64	39.3
134	39.5	54	93		38.1
184	38.0	41	81		38.0
198	38.4	87	132		39.4
213	40.4	88	111		39.0
Average	39.4	68	108	—	38.9

*Oral temperature

Chloroquine -- Responsive Vivax Malaria in Thailand: Although vivax malaria is not always radically cured by chloroquine and primaquine, the acute clinical attack does respond to chloroquine alone. Since falciparum malaria in Thailand is highly resistant to chloroquine, we wished to confirm the sensitivity of vivax malaria to this drug.

Patients with clinically severe vivax malaria and microscopic confirmation of a pure infection were selected for study. Patients with mixed infections of *P. falciparum* and *P. vivax* were separately studied.

All of 10 patients with vivax malaria responded rapidly to chloroquine (Table 3). The mean fever clearance time was 44 hours compared to 64 hours for falciparum malaria treated with quinine at the same hospital. The mean parasite clearance time was 44 hours compared to 69 hours for falciparum malaria treated with quinine. The parasitemia remained negative in the patients who completed the 28 day follow-up.

The rapid action of chloroquine in acute attacks of vivax malaria was confirmed in an area where falciparum malaria is highly resistant to this drug.

Table 3. Vivax Malaria Treated with Chloroquine: Initial Clinical Response

Case Number	Asexual Count (per cmm)	Parasite Clearance Time (Hours)	Initial Fever (°C)	Fever Clearance Time (Hours)
1	11040	37	38.8	35
2	8100	47	37.2	—
3	24570	52	41.0	56
4	14023	47	39.8	—
5	4540	62	40.5	38
6	14580	44	40.6	—
7	17063	42	37.9	—
8	7614	44	40.0	43
9	7000	40	39.0	40
10	5265	24	39.6	28
Average	11379	44	39.4	40

Jaundice in Falciparum Malaria: Over a 2 month interval sera were taken from a group of outpatients with malaria at Trad Provincial Hospital. The Department of Biochemistry, SEATO Medical Research Laboratory kindly performed biochemical determinations. Sera of 235 patients with falciparum malaria were examined. 79% had a serum total bilirubin below 2 mg% and did not have clinically visible jaundice (Table 4). 21% of the patients had increased serum bilirubin. 14% of all the patients had mild biochemical jaundice (bilirubin between 2 and 4 mg%); 5% had moderate jaundice (bilirubin between 4 and 10 mg%);

and 2% had severe clinical and biochemical jaundice (bilirubin over 10 mg%). There was a positive correlation between the parasite count and the bilirubin level (Table 5), a finding which we had expected. The fact that jaundice in malaria is related to the severity of the infection is confirmed by analysis of 11 patients recently studied (Table 6).

We also studied a group of 24 patients with vivax malaria. The mean total bilirubin level was only 0.99 mg%. The highest single value was 1.7 mg%.

Most falciparum patients with jaundice have a high parasitemia and require urgent intravenous antimalarial therapy. Quinine is the only effective drug available; however, the jaundice may indicate liver damage. Quinine is metabolized by the liver and can be toxic to that organ. Quinine toxicity may be induced even with orthodox dosages. Over the first 24 hours optimum therapy is usually 20 gr quinine in 1000 ml saline given as 2 separate infusions of 500 ml. The infusion rate should not exceed 100 ml per hour. A similar regimen can be given on succeeding days. The quinine should be given orally when the patient has improved. Radical cure of these patients is difficult and oral therapy should be prolonged; however, the patients are usually fit for discharge before the jaundice has cleared.

Table 4. Incidence of Jaundice in 235 Patients with Falciparum Malaria

Total Bilirubin (mg percent)	Number of Patients	% of Total	Diagnosis
0-2	186	79	No Jaundice
2-4	33	14	Mild Jaundice
4-10	12	5	Moderate Jaundice
10+	4	2	Severe Jaundice

Table 5. Correlation of Parasite Counts with Bilirubin Levels in Falciparum Malaria

Range of Asexual Parasite Count*	Number of Patients	Mean Total Bilirubin mg% (\pm Standard error)
0-100	16	0.91 \pm 0.15
100-1000	22	0.92 \pm 0.10
1000-10,000	66	1.33 \pm 0.11
10,000-100,000	100	1.62 \pm 0.18
100,000+	31	3.36 \pm 0.74

* Parasites per cmm

Table 6. Patients with Falciparum Malaria and Clinical Jaundice

Case Number	Asexual Parasite Count*	Total Bilirubin mg%
1	109382	32
2	53508	39
3	2106	11
4	16686	8
5	96288	28
6	7720	7
7	437710	8
8	131606	21
9	546000	11
10	46656	12
11	146692	9
Average	144,941	17

* Per cmm

Management of Anemia in Falciparum Malaria: In many patients with falciparum malaria, pulmonary edema and hemoglobinuria have followed blood transfusion. We have successfully managed several patients without blood transfusion and wish to record our findings.

In our patients with malaria, we define the anemia as severe if the hematocrit (packed cell volume) is below 15%. Anemias with hematocrits above this level seldom require special attention. We have recently conservatively managed 5 patients with hematocrits that fell below 15% (Table 7). In most patients the lowest hematocrit was recorded a few days after admission. None of the patients developed cardiac failure. They all received quinine therapy initially by the intravenous route. Infusions were given slowly. Slow but steady progress was observed in all cases. Radical cure was achieved in the 3 patients who were followed-up. None of the patients developed pulmonary edema or hemoglobinuria.

We have not yet treated an anemic falciparum malaria patient by blood transfusion. We consider that eradication of the parasitemia is of prime importance but that, because of the weakened state of the patients, the antimalarial therapy should be given cautiously, usually at reduced dosage. Criteria for blood transfusion might be a hematocrit below 10%, cardiac failure or failure to improve; however, we think that blood transfusion is very seldom indicated in falciparum malaria.

Intravenous Overload, Pulmonary Edema and Coma in Falciparum Malaria: It has been reported that pulmonary edema is a specific complication of falciparum malaria; however, most cases of pulmonary edema reported in recent years and those seen by us at Trad have followed the administration of large volumes of intravenous fluids. We have studied fluid balance in seriously ill malaria patients.

Table 7. Patients with Falciparum Malaria and Hematocrits below 15%.
Blood Transfusions not Given.

Case Number	Initial Parasite Count*	Lowest Hematocrit	Final Result
1	577,850	14 %	Radical Cure
2	22,194	13 %	Radical Cure
3	24,240	13 %	No Follow-up
4	138,200	12 %	Radical Cure
5	4,212	11 %	No Follow-up
Average	153,339	13 %	—

* Per cmm

During the last 15 months at Trad we have seen 5 malaria patients who developed pulmonary edema and coma. We considered that these patients may have been given excessive amounts of intravenous fluids in the first 24 hours (Table 8); on average they received 2490 ml (range 2000–3000 ml). In most instances each 500 ml contained 10 gr quinine. Intravenous fluid overload may have contributed to the pulmonary edema and coma, and quinine overdosage probably also occurred in some instances.

Subsequently, we decided to limit intravenous fluid therapy to not more than 500 ml in any 8 hour interval. Five patients were treated with this regimen (Table 9), and pulmonary edema did not occur. One death occurred, but this can be attributed to the poor condition of the patient upon hospital admission. The average intake of fluid in the first 24 hours was 1500 ml (range 1000–2000 ml).

Table 8. Falciparum Malaria with Coma. Pulmonary Edema Attributed to Intravenous Overhydration in First 24 Hours

Case Number	Initial Parasite Count (per cmm)	Age (Years)	IV Fluids (ml) Infused in Time Interval (Hours)			Total (ml) 24 Hours	Comment
			0–8	8–16	16–24		
1	317,844	20	1450	0	1000	2450	
2	94,640	30	2000	0	1000	3000	death
3	601,640	30	1650	350	1000	3000	
4	318,000	16	1500	0	500	2000	death
5	777,600	22	1000	500	500	2000	
Average	421,600	24	1520	170	800	2490	

Table 9. Falciparum Malaria with Coma. Absence of Pulmonary Edema Attributed to Optimal Intravenous Hydration in First 24 Hours.

Case Number	Initial Parasite Count**	Age (Years)	IV Fluids (ml) Infused In Time Interval (Hours)			Total (ml) 24 Hours	Comment
			0-8	8-16	16-24		
6	109,382	35	1000	0	1000	2000	
7	2,997	16	900	100	0	1000	
8	307,638	30	630	370	500	1500	
9	26,568	45	500	500	500	1500	death*
10	22,295	24	500	500	500	1500	
Average	93,776	30	706	294	500	1500	

* Patient moribund on admission.

** Parasites per cmm

Nevertheless, with this limited intravenous fluid regimen, 30 gr of quinine are still being infused in 24 hours. We think this may be too much in patients with very high parasite counts or who are in deep coma. 20 gr may be more suitable daily dose in these patients.

We conclude that coma and pulmonary edema in falciparum malaria are often caused by or exacerbated by excessive intravenous infusion of fluids.