

Amodiaquine Resistant *Falciparum* Malaria In Thailand

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OBJECTIVE: To determine the comparative efficacy of amodiaquine and chloroquine against *falciparum* malaria in Thailand.

BACKGROUND: Interest in 4-aminoquinolines other than chloroquine was reawakened by Schmidt as quoted by Rieckmann, (1) who found in owl monkeys that two chloroquine-resistant strains of *P. falciparum* were more susceptible to amodiaquine than to chloroquine. Rieckmann obtained similar findings both *in vitro* and *in vivo* although radical cures were not achieved in volunteers. Fitch demonstrated that owl monkey erythrocytes infected with chloroquine resistant *P. falciparum* had a deficiency of chloroquine-¹⁴C uptake, but not deficiency of amodiaquine-¹⁴C uptake (2). Therefore, we compared the therapeutic efficacy of the two drugs in a chloroquine-resistant endemic area. Preliminary results of this study have been tabulated (3).

DESCRIPTION: The study was performed at Trad Hospital in Southeast Thailand in 1973 and 1974. Details of the research methods have recently been given (3). The area is forested and malaria is endemic throughout the year. Chloroquine given either orally or parenterally (but not amodiaquine) is used frequently to treat patients with the clinical diagnosis of malaria. Chemoprophylaxis is not practiced in the community. All patients were fully informed on the nature of the drug trial and consent was granted voluntarily. They all had mild or moderate *falciparum* malaria and an asexual count greater than 1,000 per cu.mm. Alternate patients were assigned to chloroquine or amodiaquine. Chloroquine is 7-chloro-4 (4'-diethylamino-1'-methyl butylamino) quinoline. The dosage form used was not enteric coated ("Nivaquine" tablets by May and Baker which contained 150 mg of chloroquine base). Amodiaquine is 7-chloro-4 (3, diethylamino methyl 1-4,-hydroxyanilino) quinoline, and the dosage form was a non-enteric coated tablet (Camoquine by Parke-Davis) which contained 200 mg of the base. A 1.5 g course of both drugs was administered during three days; 600 mg on the first day was followed by 300 mg six hours later and 300 mg on each of the succeeding two days.

Because only a minority of patients were cured by 1.5 g of amodiaquine given during three days, a 2.0 g course during four days was studied in an additional group of patients. Most patients received 400 mg (two tablets) initially followed by 400 mg six hours later on day 0, then 400 mg on the mornings of days 1, 2 and 3. All medications were administered by the study physicians.

Direct quantitative parasite counts (4) were performed before treatment, twice daily in hospital for at least three days and on days 14, 21 and 28 from the beginning of therapy. Daily hematocrits and leukocyte counts were done. Fifty milliliters of urine were obtained daily and frozen. The specimens were later analyzed for amino-quinoline content. Ten milliliters of urine (ph 8.3) were extracted with 25 ml of a 4:1 solvent of chloroform and isopropanol. Ten grams of anhydrous sodium sulfate were then added to the extract and the solutions filtered. The dried filtrates were dissolved in a few drops of methanol and then spotted on TLC plates precoated with silica gel. The plates were developed with a mixture of ethyl acetate, methanol and ammonium hydroxide (85:10:5) and then sprayed with acidified iodoplatinate. Control urines containing added chloroquine or amodiaquine were processed similarly and used as standards. The R_f for chloroquine was 0.85 and for amodiaquine was 0.96.

CHLOROQUINE 1.5 g. In hospital, chloroquine cleared parasitemia in only three of the 13 patients (Table 1) despite the mildness of many of the infections (average parasite count only 13,920). One of

these men developed a recrudescence in the follow-up period; the other two could not be traced. In many patients chloroquine had little or no effect on parasitemia—a potentially dangerous situation. Therefore, treatment with chloroquine was stopped after 13 patients and the final four patients received amodiaquine. The following case history illustrates the severity of chloroquine resistance in the patients studied.

Patient No. 7: This patient had a headache, myalgia and cough on admission. There was a fever of 39.5°C. Therapy with chloroquine 600 mg was given. On the next morning another 600 mg of chloroquine was administered. His parasitemia was 8,220 which increased to 18,270 in the evening. Another 300 mg of chloroquine was given at 1600 hours. The fever increased to 40.4°C and the patient became toxic and vomited. An intravenous infusion of quinine was given and the patient had greatly improved by the next morning. A ten dose course of quinine was administered, the fever and parasitemia cleared and the patient was asymptomatic when discharged; however, a recrudescence occurred on day 26.

Comment: Chloroquine 1.5 g was followed by an RIII response and a three day course of quinine was followed by an RI response.

AMODIAQUINE 1.5 g. The average total dose for the group was 30 mg/kg compared with 28 mg/kg for the chloroquine group. The standard 1.5 g course of amodiaquine was significantly more successful ($p < 0.01$) in clearing parasitemia (15 out of 17 patients) than chloroquine (Table 2). The mean parasite clearance time was 77 hours which, in relation to the mean parasite count of only 18,000 per cu.mm., can be considered prolonged. The mean fever clearance time was 47 hours which is unusually short for an antimalarial drug in our test system.

Four patients did not attend follow-up examinations and radical cure was achieved in 38 per cent (5/13) of the remainder. This is not a successful result because most of the patients had clinically mild disease.

AMODIAQUINE 2.0 g. The average total dose for the group was 42 mg/kg. Twenty-four patients with mild to moderate disease were treated. The parasitemia was cleared in 22 men (Table 3). The mean parasite clearance time was 77 hours. The mean fever clearance time was 36 hours which was much shorter than for any other regimen that we have tested, and probably indicates that amodiaquine does not cause a drug fever. The overall cure rate of 38 per cent (8/21) was the same as was obtained with the 1.5 g course of amodiaquine in the group of patients with a lower mean parasite count (Table 4). One patient had a clear-cut RIII response and another an RII response and the case histories are described below. In eleven patients the parasitemia cleared in hospital but a recrudescence occurred after discharge.

Patient No. 34: This patient was a 34 year old gem-miner who had migrated to the highly endemic area one month previously. He was probably non-immune. He had experienced headache and myalgia for nine days and was thirsty. His parasite count was 121,125 per cu.mm. His fever was 38.5°C on the day of admission and he received 600 mg amodiaquine followed by 200 mg four hours later. Despite another 400 mg amodiaquine at 0600 hours on day 1, his parasite count increased to 207,100 and his fever increased to 39.2°C with severe clinical toxicity. One dose of intravenous quinine therapy was given and then a single dose of pyrimethamine with sulfadoxine (Fansidar). His fever and parasitemia cleared but the patient did not attend follow-up.

Patient No. 37: This patient was a 38 year old farmer who had always lived in the endemic area. Therefore, using conventional terminology, he could be considered semi-immune. He had a headache for two days and had received one injection on the day before admission. His parasite count was 97,395 per cu.mm. and fever 39.4°C. On the day of admission 600 mg of amodiaquine was administered followed by 200 mg four hours later. Five hundred milliliters dextrose-saline was infused intravenously. On day 1 his headache persisted, as did a fever of 38–39°C; the parasitemia decreased to 4,845 per cu.mm. and another 400 mg of amodiaquine was administered. On day 2, despite two more doses of amodiaquine (to complete the 2.0 g course), the fever increased to 39.6°C and his parasite count rose to 36,480. A single dose of pyrimethamine with sulfadoxine was given and the temperature rapidly fell to 37.1°C. A radical cure was achieved.

The patient's falciparum malaria was resistant at the RII level to a 2.0 g course of amodiaquine given in five doses. The infection was then radically cured by a single dose of sulfadoxine 1.5 g with pyrimethamine 75 mg.

URINES: Urine specimens were obtained before treatment from 45 patients. Chromatography of these specimens showed spots corresponding to one or both of the 4-aminoquinolines in 39. The data do indicate that a high proportion of the patients had chloroquine therapy before admission.

All 45 patients had evidence of 4-aminoquinolines in post-treatment urine specimens. Chromatographic differentiation of the two drugs was not completely accurate.

TOXICITY: Symptoms (for example, nausea, abdominal discomfort and dizziness) were frequent during chloroquine therapy and were at least partially attributed to an unsatisfactory response to treatment.

Abdominal tightness, dizziness and other symptoms were fairly common on amodiaquine therapy (although not more so than with chloroquine) and in one patient the toxicity was alarming. Patient number 45 was aged 15 and weighed only 29 kg. He received a 2.0 g course during four days. Four hours after the last dose he complained of difficulty breathing and of palpitations. His pulse was normal but he appeared distressed and slightly cyanosed and had a prominent third heart sound. At this time his parasitemia was only 48 per cu.mm.; therefore, amodiaquine toxicity was the probable diagnosis. The patient improved within a few hours.

DISCUSSION: Falciparum malaria in Thailand responds poorly to chloroquine whether given as treatment (5,6) or for suppressive prophylaxis (7). The logical deduction is that chloroquine should not be used for falciparum malaria in Thailand. In practice, chloroquine is frequently prescribed both orally and parenterally, especially in remote areas, presumably because of low cost and easy supply. Whether this is desirable is a fundamental question. We do feel that due consideration should be given to banning the use of chloroquine in countries where falciparum malaria shows severe resistance as in Thailand (where the cure rate in our study was 0 per cent).

We found that vivax malaria comprises 14 per cent of all cases of malaria in Southeast Thailand (3). However, species identification is not usually available in the local laboratories. Thus, detection of vivax malaria is not normally achieved. Chloroquine, as a 1.5 g course over three days, is the appropriate treatment for the suppression of a clinical attack of vivax malaria. But without microscopic diagnosis, the patients are unlikely to receive a full course of chloroquine. In hospital the patients with vivax malaria receive the same therapy (which does not normally include chloroquine) as those with falciparum malaria. Therefore, if chloroquine were no longer available, the patients with vivax malaria (a benign disease) would not be treated differently in hospital and the patients with falciparum malaria (a serious disease), would not be receiving this ineffective drug before admission to hospital.

Another fact that has received insufficient attention is that both parenteral chloroquine (8,9) and oral chloroquine (10, 11) can be fatal. Cardiac arrest and convulsions are two of the most serious side-effects. High prolonged dosage can cause blindness and the indications for chloroquine therapy have been drastically reduced to malarias other than chloroquine resistant *P.falciparum* and extraintestinal amebiasis (12). Children are especially sensitive to the 4-aminoquinoline compounds. Amodiaquine can cause agranulocytosis (13) as well as toxicity similar to chloroquine. Fortunately in the treatment of malaria, 4-aminoquinolines by the oral route are relatively safe, especially in adults.

We found (Table 4) that amodiaquine (38 per cent cure rate) was more effective (Chi square = 4.16, $p < 0.05$) than chloroquine (0 per cent) in the treatment of chloroquine-resistant falciparum malaria. The predominant response was RI rather than RII. However, the cure rate of 38 per cent with multi-dose amodiaquine is not very impressive when compared with the 85 per cent cure rate we obtained with a single dose of pyrimethamine with sulfadoxine (14). The cure rates are significantly different (Chi square

=14.8, $P < 0.01$). In the treatment of falciparum malaria in Thailand, quinine (3) or pyrimethamine with sulfadoxine (14, 15) are more effective than amodiaquine. Therefore, there is no clear-cut indication for amodiaquine in the treatment of falciparum malaria in Thailand. Amodiaquine might have an occasional role in patients who show hypersensitivity to quinine. But amodiaquine alone would not be satisfactory, since so many recrudescences occur. Following the initial course of amodiaquine, alternate therapy, such as a single dose of pyrimethamine with sulfadoxine, would be needed to prevent a recrudescence.

The fever clearance time was unusually short for amodiaquine compared with other antimalarial drugs which suggests that amodiaquine does not cause a drug fever.

The difference in cure rates between amodiaquine and chloroquine may be partly explained by the fact that chloroquine is widely used in Thailand whereas amodiaquine is not used at all. The falciparum parasites are probably resistant to 4-aminoquinolines in general but have not acquired a specific resistance to amodiaquine. Amodiaquine resistant falciparum malaria has also been detected in the Philippines where amodiaquine is used (16).

SUMMARY: Amodiaquine cured 38 per cent (13/34) of patients with falciparum malaria in Southeast Thailand. Chloroquine cured 0 per cent (0/13). The cure rates with amodiaquine were the same whether a 1.5 g or 2.0 g course was used. Most patients were resistant to amodiaquine at the RI level and to chloroquine at the RII level. In hospital amodiaquine cleared parasitemia more frequently than did chloroquine. With the 2.0 g course of amodiaquine, the parasite clearance time was 77 hours; the fever clearance time of 36 hours was short and suggests that amodiaquine does not cause a drug fever.

Because of resistance, chloroquine should not be used for falciparum malaria in Thailand. Routine use of amodiaquine is not indicated because more effective drugs are available.

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Table 1. Falciparum Malaria in Thailand. Therapy with 1.5 g Chloroquine over Three Days

Patient Number	Asexual Count <i>P. falciparum</i> (per cu.mm.)	Parasite Clearance Time (hours)	Initial Fever (°C)	Fever** Clearance Time (hours)	Result***	Comment
1	49572	—	38.5	—	RII	
2	27391	—	37.2	—	RII	
3	21021	—	38.8	52	RII	
4	20637	—	40.2	—	RII	
5	18200	69	36.8	—	—	
6	13160	—	40.0	—	RIII	
7	12820*	—	39.5	—	RIII	
8	6552	—	39.0	51	RII	
9	3240	—	37.7	—	RII	
10	2710	41	39.0	63	RI	
11	2340	—	37.5	—	RII	
12	1820	68	37.7	—	—	
13	1500	—	38.8	74	RII	
Mean	13920	N/A	38.5	N/A		Cure Rate=0% (0/11)

* Median count

** Fever clearance time not computed if initial fever 38.0°C

*** If no symbol, final result could not be determined. RIII, no marked reduction of asexual parasitemia; RII, marked reduction of asexual parasitemia, but no clearance; RI, clearance of asexual parasitemia, followed by recrudescence; S, clearance of asexual parasitemia without recrudescence (radical cure). World Health Organization (1967) Tech. Rep. Ser., No. 375, p.42.

Table 2. *Falciparum* Malaria in Thailand. Therapy with 1.5 g. Amodiaquine over Three Days

Patient Number	Asexual Count <i>P. falciparum</i> (Per cu.mm.)	Fever Clearance Time (hours)	Initial Fever (°C)	Fever Clearance Time (hours)	Result	Comment	
14	54000	70	40.3	86	S	<i>P. vivax</i> Day 45	
15	35900	—	37.9	—	RII		
16	34830	60	39.5	46	S		
17	21060	75	38.0	43	—		
18	20000	69	38.0	56	RI		
19	18428	70	37.3	—	RI		
20	18425	—	38.6	55	RII		
21	18200	100	38.2	20	S		
22	14256*	93	39.5	19	—		
23	13190	117	39.0	79	RI		<i>P. vivax</i> Day 44
24	12376	76	37.7	—	RI		
25	9100	48	37.6	—	S		
26	9100	65	39.7	13	—		
27	8730	90	37.5	—	RI		
28	7917	47	37.5	—	S		
29	7735	105	39.4	55	RI		
30	4320	66	37.7	—	—		
Mean	18092	77	38.4	47		Cure Rate=38% (5/13 followed-up cases)	

* Median count

Table 3. *Falciparum* Malaria in Thailand. Therapy with 2.0 g Amodiaquine over Four Days

Patient Number	Asexual Count <i>P. falciparum</i> (per cu.mm.)	Parasite Clearance Time (hours)	Initial Fever (°C)	Parasite Clearance Time (hours)	Result	Comment
31	168720	—	39.8	64	S	
32	152000	85	39.8	60	RI	
33	149670	—	37.9	—	RI	
34	121125	—	38.5	—	RIII	
35	102980	88	37.4	—	RI**	
36	102600	—	38.4	40	S	
37	97395	—	39.4	—	RII**	
38	91960	86	39.7	61	RI	
39	65930	59	39.2	22	—	
40	63175	—	40.3	56	RI	
41	51680	—	39.3	6	RI	
42	48070*	116	38.2	43	RI	
43	45410	—	39.3	20	S	
44	42180	—	39.1	45	RI	
45	21140	75	39.8	43	—	
46	21090	87	38.6	14	RI	
47	16562	115	39.4	—	RI	
48	9696	88	37.3	—	RI	
49	7392	94	37.7	—	S	
50	5265	43	37.2	—	S	
51	4050	63	39.6	14	—	
52	3680	41	37.7	—	S	
53	2916	67	40.0	42	S	
54	2700	41	38.9	32	S	
Mean	58,228	77	38.9	36	Radical Cure Rate=38% (8/21)	

* Median count

** Cured by single dose pyrimethamine with sulfadoxine

Table 4. Comparison of Cure Rates

Drug	Mean Parasite Count (per cu.mm.)	RIII	RII	RI	S	Total	Cure* Rate
Chloroquine 1.5 g	14000	2	8	1	0	11	0 %
Amodiaquine 1.5 g	18000	0	2	6	5	13	38 %
Amodiaquine 2.0 g	58000	1	1	11	8	21	38 %

* Difference between cure rates for amodiaquine and chloroquine is significant ($\chi_2 = 4.23, p < 0.05$)