

Falciparum Malaria Semi-resistant to Clindamycin

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BACKGROUND: The antimalarial activity of a group of chlorinated lincomycin analogues was first demonstrated in mice infected with *P. berghei* (6,9) and in monkeys infected with *P. cynomolgi* (9,11). Schizontocidal as well as causal prophylactic and radical curative activity was observed. Chloroquine-resistant *P. falciparum* infections in owl monkeys were also cured by these compounds (10). Both in animals and in man infected with malaria, clindamycin acted slowly; however, three day courses of quinine and clindamycin given in combination or sequentially proved effective against chloroquine-resistant falciparum malaria in volunteers (7). We tested clindamycin alone and in combination with quinine in Thais naturally infected with chloroquine-resistant falciparum malaria.

DESCRIPTION: The study was performed at the Trad Provincial Hospital in Southeast Thailand. Details of the research methods have been described (4). We operated a daily malaria clinic at the hospital and suitable outpatients volunteered for the inpatient studies. Informed consent was obtained in all cases. Male patients with an asexual parasite count over 1,000 per cu.mm. were included. To avoid the problem of immunity, patients with clinically mild infections were rarely studied.

Quantitative parasite counts were made at least twice daily in hospital on blood specimens obtained by finger-prick taken at 0700 and 1400 hours and at follow-up examinations on days 14, 21 and 28. Determination of the hematocrit (packed cell volume) and leukocyte count was made on admission and whenever clinically indicated. Sera were collected on admission and the concentrations of bilirubin and creatinine determined.

Throughout the study, the drugs were administered by one of the study physicians during medication-ward rounds usually made at 0600, 1400 and 2100 hours. The patients were observed by the physician as they swallowed the drug with water, then examined and kept under observation for a few minutes. The clindamycin was dispensed as 150 mg capsules (Cleocin, Upjohn) and the usual dose was 450 mg every 8 hours for three days (total dose 4050 mg). The quinine was administered as sugar-coated tablets of quinine sulfate, USP each containing 270 mg base. The usual dose was 540 mg every 8 hours for three days (total dose, 4860 mg).

Follow-up examinations on days 14, 21 and 28 were made either in the clinic or at home.

In the evaluation of the final therapeutic result in each patient, the WHO (14) classification was used (Table 1). A radical cure was diagnosed if the parasitemia was cleared and had not reappeared before day 29. Parasite clearance times were calculated in hours. Fever clearance times were computed in hours if the initial fever was at least 38.0°C. Clearance was diagnosed when the temperature decreased to 37.2°C or less and remained at this level for at least one more reading. If there was still fever or parasitemia on discharge at least 100 hours after admission, the elapsed time was arbitrarily counted as the clearance time.

CLINDAMYCIN: Eleven patients were treated with 450 mg every 8 hours for three days. One patient (Case No. 4) was a 12 year old boy weighing 28 kg. He received 300 mg every 8 hours. In five patients not responding to clindamycin, the drug was stopped and more effective therapy given.

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The initial clinical response was fairly rapid in some of the patients (Table 1) but the mean parasite clearance time was prolonged (88 hours) as was the fever clearance time (68 hours).

In five patients the parasitemia was cleared and did not reappear on follow-up examination on days 14, 21 and 28. These patients were adjudged to be radically cured. The average initial parasite count in these five patients (33269 per cu.mm.) was less than that (73511 per cu.mm.) in the five patients who were not cured (the difference was not statistically significant). In two other patients (Cases 2 and 6) an initial clinical response occurred but follow-up was not achieved. Thus the initial clinical response was satisfactory in seven of the 12 patients.

In five patients the initial infection was not controlled by clindamycin and because of a worsening clinical and parasitemic situation, alternate therapy had to be given. Two of these patients were cured by sequential therapy with quinine and Fansidar (pyrimethamine and sulfadoxine). Two other patients were cured by a single dose of Fansidar given alone. The case-history in one of these patients is described below. A clinical response to Fansidar occurred in the fifth patient but follow-up was not obtained. Thus the overall cure rate for clindamycin was 50% (5/10).

No clear-cut toxicity due to clindamycin occurred in these patients; however, Case No. 2 had persistent dizziness and weakness during therapy and tinnitus occurred for two days afterwards.

Case No. 12: The patient was a 43 year old farmer born locally. The main symptom was a headache for four days. He had received two intramuscular injections (content unknown) on the day before admission. He was in distress with a fever of 40.0°C, although his parasitemia was only 8265 per cu.mm. Clindamycin 450 mg was administered at 1600 and 2100 on day 0 and thereafter every eight hours. The fever abated briefly on the morning of day 1 but then returned to 40.0°C. The parasitemia decreased to 665 on day 1 but then rose to 9880 on day 2. On the evening of day 2, because of the increase in parasitemia, the high fever (40.0°C) and persistent severe symptoms, drug failure (R11 type) was diagnosed. Seven doses of clindamycin had been given. The patient then received a single dose of Fansidar (sulfadoxine 1.5 g with pyrimethamine 75 mg). The parasitemia then cleared in 48 hours and the fever in 60 hours. Blood films were negative on days 13, 21 and 30 and a radical cure was diagnosed.

QUININE WITH CLINDAMYCIN (FULL DOSAGE): Six patients were begun on treatment with quinine 540 mg base every 8 hours and clindamycin 450 mg every 8 hours given at the same time for three days (Table 2). The dosage of clindamycin was reduced (usually to 300 mg) in most patients because of intolerance.

In five of the six patients, the quinine-clindamycin combination appeared to cause toxicity. In Case No. 13; his symptoms worsened during therapy but improved when the clindamycin was stopped. In Case No. 15; despite a fall in parasite count from 55,419 to 40, he developed severe anorexia after the sixth dose of clindamycin. Cases No. 16, 17 and 18 had a similar clinical picture; they developed severe retching one to four hours after the second to fourth dose of quinine and clindamycin. They all improved after the clindamycin was stopped despite the continuation of the quinine at full dosage. After the course of quinine was finished and the patients had improved, clindamycin was resumed without causing any side effects when given alone.

Four patients were cured and two others did not complete follow-up. The mean parasite clearance time was prolonged (83 hours) and the mean fever clearance time was 67 hours.

QUININE WITH CLINDAMYCIN (HALF DOSAGE): Eight patients received combination therapy with half dose quinine (270 mg) and approximately half-dose clindamycin (150 mg) every 8 hours (Table 3). The mean parasite clearance time was prolonged (95 hours) and the mean fever clearance time was 68 hours. Complete follow-up was achieved in five patients of whom three were cured (60%). A clinical response occurred in two other patients but follow-up was not achieved. The eighth patient (Case No. 22)

developed toxicity after four doses of therapy and was then treated with quinine followed by Fansidar. Five of the eight patients developed unacceptable toxicity which consisted mainly of upper gastrointestinal symptoms. Details of three of these cases are given.

Case No. 19: This patient received four full doses of quinine (three intravenously) without toxicity. He then received quinine with clindamycin at half dosage. After two doses the patient developed nausea, tightness in the chest and severe retching which persisted for eight hours. The clindamycin was stopped. The symptoms improved although the quinine therapy was continued. After the nine dose course of quinine had been completed, the clindamycin was resumed until nine doses had been given. The patient had persistent weakness during this time. The parasitemia and fever cleared but follow-up until day 28 was not obtained.

Case No. 20: This patient received five full doses of quinine at eight hour intervals uneventfully. Then the semi-dose combination was given for two doses. The patient felt generally worse and a persistent fever developed. The clindamycin was stopped and also the quinine after two more doses. Sixteen hours later when he felt better the clindamycin was resumed for five doses during which time the patient felt listless. A radical cure was achieved.

Case No. 22: The patient was virtually asymptomatic on admission, having mild headache and backache only. After two doses of quinine 540 mg and clindamycin 300 mg at 1000 and 2100 hours on day 0, he developed nausea and vomiting, headache, dizziness and prostration. On day 1 he received quinine 270 mg and clindamycin 150 mg at 0600 and 1400. The patient remained very toxic with weakness and dizziness although the parasite count had fallen from 60,000 to 650 per cu.mm. The clindamycin was stopped but the quinine was continued and the dose increased to 540 mg; the patient improved and remained well. After 12 doses of quinine, a single dose of Fansidar was given. The patient was cured.

QUININE ALONE: Three patients were treated with a three day course of quinine alone. They developed recrudescences on days 14, 22 and 25, respectively (Table 4).

TETRACYCLINE ALONE: Four patients received tetracycline 250 mg every 6 hours for three days (Table 5). Two patients had an RIII response and one patient had an RII response. A slow clearance of parasitemia occurred in the fourth patient but follow-up was not obtained.

DISCUSSION: *Falciparum malaria* in Thailand is difficult to eradicate in many patients. In recent studies the cure rate with chloroquine (5) or with pyrimethamine (3) was 0%. This data indicates that clindamycin is partially effective against chloroquine-resistant *falciparum malaria* in patients with clinically moderate disease. In some men the clinical response to clindamycin was rapid but in others it was slow or ephemeral. Our cure rate of 50% with multi-dose clindamycin compares with the 85% cure rate we obtained with a single dose of pyrimethamine with sulfadoxine (3). The average parasite clearance time for clindamycin (88 hours) was significantly longer ($p < 0.05$) than that for pyrimethamine with sulfadoxine (71 hours). Wagner et al. (13) found that clindamycin has a short half-life of only 2.4 hours and consequently, frequent doses must be given which is a disadvantage in the treatment of malaria. On the other hand sulfadoxine has a half-life of about 200 hours as determined by Brooks et al. (1). In our test system clindamycin was obviously a more powerful antimalarial than tetracycline (Table 5).

Clindamycin alone was not toxic in our patients; however, several recent reports have shown that lincomycin or clindamycin (a chlorinated lincomycin analogue) can cause ulcerative colitis or even pseudomembranous colitis (2, 8, 12). The diarrhea usually begins after 4 to 9 days of therapy. Colitis was not detected in our patients. Clindamycin is probably the most potent antimalarial among the antibiotics. However, because of its partial efficacy and potential toxicity, clindamycin alone has a limited role as an antimalarial.

Quinine and clindamycin in combination at full or half dosage apparently potentiated toxicity in our patients. Retching and frank vomiting were frequently observed, although Miller et al. (7) did not encounter gastrointestinal intolerance. Other patients had less specific symptoms and did not look well.

When the clindamycin was stopped but the quinine continued, the patients improved. Likewise when the course of quinine had been completed, clindamycin alone did not cause serious side-effects. The therapeutic results with full dose quinine and clindamycin therapy were excellent (4/4 cures). Perhaps quinine and clindamycin potentiate both antimalarial efficacy and toxicity.

Sequential administration of quinine and clindamycin was not toxic and could be useful in patients who have relapsed following more conventional therapy (e.g. quinine followed by Fansidar).

By studying high count rather than low count cases, we produced a more severe test of antimalarial efficacy in any regimen studied i.e, the degree of "drug pressure" was increased. If patients with counts only over 50,000 per cu.mm. and uncomplicated disease are selected for drug trials, comparative studies can be completed using fewer subjects. We have adopted this system without risk to the patients.

SUMMARY: Clindamycin, a semi-synthetic antibiotic of the lincomycin family, at a dose of 450 mg every 8 hours for three days in adults, cured 50% (5/10) of patients moderately ill with chloroquine-resistant falciparum malaria. Combination therapy with full dose quinine and clindamycin for three days was curative in 100% (four patients) and with half-dosage in 60% (3/5). However both combinations caused upper gastrointestinal toxicity and appeared to potentiate both toxicity and possibly antimalarial efficacy. Colitis due to clindamycin was not observed. Sequential therapy was not toxic and could be useful in patients who have recrudesced following more conventional therapy.

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Table 1. Falciparum Malaria Therapy with Clindamycin Every 8 Hours for 3 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	162260	—**	39.8	—	RIII	Cured by Quinine and Fansidar
2	93670	99	39.9	55	—	
3	82080	87	40.4	63	S	
4	77900	—	37.9	—	RII	
5	72770	—	40.5	—	RII	
6	51300	—	40.2	54	—	
7	46360*	—	40.0	—	RII	Cured by Fansidar
8	33060	97	40.0	102+	S	Cured by Fansidar
9	20140	88	40.7	63	S	
10	18144	92	39.9	76	S	
11	12920	67	40.0	66	S	
12	8265	—	40.0	—	RIII	
MEAN	56572	88	40.0	68	Radical Cure Rate=50% (5/10)	

* Approximately the median count.

** If no symbol, final result could not be determined. RIII, no marked reduction of asexual parasitemia, but no clearance; 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).

Table 2. Falciparum Malaria Therapy with Quinine and Clindamycin Both Given Every 8 Hours for 3 Days at Full Dosage

Patient Number	Asexual Count <i>P. falciparum</i> (per cu.mm.)	Parasite Clearance Time (Hours)	Initial Fever (°C)	Fever Clearance Time (Hours)	Result	Comment
13	146692	117	38.3	82	S	Drug Toxicity
14	101556	93	39.6	60	S	
15	55419	64	40.0	39	S	
16	33943*	85	40.6	60	—	Vomiting
17	8645	69	40.0	69	—	Vomiting
18	5642	69	40.0	92	S	Vomiting
MEAN	58,650	83	39.8	67	Radical Cure Rate = 100% (4/4)	

* Approximately the median count

Table 3. Falciparum Malaria Therapy with Quinine and Clindamycin Both Given Every 8 Hours for 3 Days at Half Dosage

Patient Number	Asexual Count <i>P. falciparum</i> (per cu.mm.)	Parasite Clearance Time (Hours)	Initial fever (°C)	Fever Clearance Time (Hours)	Result	Comment
19	358,830	119	37.5	99	—	Vomiting
20	236,600	116	39.1	115+	S	Drug fever
21	214,760	115	38.5	42	RI	
22	61,880	—	38.0	—	—	Toxicity
23	54,432*	67	39.9	18	S	
24	13,312	92	38.9	32	—	Vomiting
25	4,914	96	40.2	112+	S	Abdominal pain
26	2,730	59	40.9	58	RI	
MEAN	118,432	95	39.1	68	Radical Cure Rate = 60% (3/5)	

* Approximately the median count

Table 4. *Falciparum* Malaria Therapy with Quinine
Every 8 Hours for 3 Days*

Patient Number	Asexual Count <i>P. falciparum</i> (per cu.mm.)	Parasite Clearance Time (Hours)	Initial Fever (°C)	Fever Clearance Time (Hours)	Result
27	87,804	84	37.9	—	RI
28	21,708	69	39.8	—	RI
29	18,270	68	40.5	84	RI
MEAN	42,594	74	39.4	—	

Table 5. *Falciparum* Malaria Therapeutic Results in Patients
Treated with Clindamycin or Tetracycline*

Regimen	Duration Therapy	Average Parasitemia	RIII	RII	RI	S
Clindamycin	3 Days	53389	1	4	0	5
Tetracycline**	3 Days	20647	2	1	—	—

* Clinically clindamycin was more effective than tetracycline.

** One patient responded in hospital but follow-up was not achieved.