patients at risk. A larger blind study of pre-eclamptic cases is now in progress with another centre to try to relate the levels to the severity of the condition and to the wellbeing of the fetus.

DCMP deaminase is excreted in both maternal and fetal urines. Maternal and cord sera levels in both caesarean section cases and normal deliveries seemed to be quite independent of each other. The rise in the maternal serum during labour did not seem to be related to the length or severity of labour. The amniotic-fluid levels were also not related to the maternal or cord levels.

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Falciparum Malaria Semi-resistant to Clindamycin

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Summary

Clindamycin, a semi-synthetic antibiotic of the lincomycin family, at a dose of 450 mg eight-hourly for three days in adults cured five out of 10 patients moderately ill with chloroquine-resistant falciparum malaria. Combination therapy with full-dose quinine and clindamycin for three days cured all four patients so treated who were followed up, and with half dosage three out of five patients were cured. Both combinations, however, 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 relapsed after more conventional treatment.

Introduction

Chloroquine-resistant falciparum malaria responds to few drugs and new drugs are needed. The antimalarial activity of a group of chlorinated lincomycin analogues was first demonstrated in mice infected with *Plasmodium berghei* (Lewis, 1968) and in monkeys infected with *P. cynomolgi* (Powers, 1969; Schmidt *et al.*, 1970). Chloroquine-resistant *P. falciparum* infections in owl monkeys were also cured by these compounds (Powers and Jacobs, 1972). Both in animals and in man infected with malaria clindamycin acted slowly (Miller *et al.*, 1974). Three day courses of quinine and clindamycin given in combination or sequentially, however, proved effective against chloroquine-resistant falciparum malaria in volunteers (Miller *et al.*, 1974). We tested clindamycin alone and in combination with quinine in Thais naturally infected with chloroquine-resistant falciparum malaria.

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Methods

The study was performed at the Trad Provincial Hospital in south-east Thailand. The research methods have been described elsewhere (Hall *et al.*, 1975 a). We operated a daily malaria clinic at the hospital and suitable outpatients volunteered for the inpatient studies. Male patients with an asexual parasite count over 1×10^9/l were included. Informed consent was obtained in all cases. 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 at 07.00 and 14.00 hours and at follow-up examinations on days 14, 21, and 28. Determination of the packed cell volume and leucocyte 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 at 06.00, 14.00, and 21.00 hours. The patients were observed by the physician as they swallowed the drug with water and then examined and kept under observation for a few minutes. The clindamycin was dispensed as 150-mg capsules, the usual dose being 450 mg every eight hours for three days (total dose 4050 mg). The quinine was administered as sugar-coated tablets of quinine sulphate (*U.S.P.*), each containing 270 mg base. The usual dose was 540 mg every eight 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 evaluating the final therapeutic result in each patient the W.H.O. (1967) classification was used (see table I). A patient was regarded as radically cured when the parasitaemia was cleared and had not reappeared before day 29. Parasite clearance times were measured in hours. Fever clearance times were measured (in hours) when the initial fever was at least 38·0°C. Clearance of fever was so defined when the temperature fell to 37·2°C or less and remained at that level for at least one more reading. If the fever or parasitaemia persisted at the time of discharge at least 100 hours after admission the elapsed time was arbitrarily regarded as the clearance time.

Results

CLINDAMYCIN

Twelve patients (cases 1–12) were treated with clindamycin alone (table I); 11 received 450 mg every eight hours for three days, and one (case 4), a 12-year-old boy weighing 28 kg, received 300 mg every eight hours. In five patients not responding to clindamycin a more effective regimen was substituted.

The initial clinical response was fairly rapid in some of the patients (table I) but the mean parasite and fever clearance times were slow (88 and 68 hours respectively). In five patients

TABLE I—*Results of Treatment in 29 Patients with Falciparum Malaria*

Case No.	Asexual Count of *P. Falciparum* ($\times 10^9$/l)	Parasite Clearance Time (h)	Initial Fever (°C)	Fever Clearance Time (h)	Result†	Comment
			Clindamycin eight-hourly for three Days			
1	162·260		39·8		RIII	Cured by quinine and Fansidar
2	93·670	99	39·9	55		
3	82·080	87	40·4	63	S	
4	77·900		37·9		RII	Cured by quinine and Fansidar
5	72·770		40·5		RII	
6	51·300		40·2	54		
7	46·360*		40·0		RII	Cured by Fansidar
8	33·060	97	40·0	102+	S	
9	20·140	88	40·7	63	S	
10	18·144	92	39·9	76	S	
11	12·920	67	40·4	66	S	
12	8·265		40·0		RII	Cured by Fansidar
Mean	56·572	88	40·0	68	Radical cure rate 50% (5/10)	
			Quinine and Clindamycin eight-hourly for three Days at Full Dosage			
13	146·692	117	38·3	82	S	Drug toxicity
14	101·556	93	39·6	60	S	
15	55·419	64	40·0	39	S	Anorexia
16	33·943*	85	40·6	60		Vomiting
17	8·645	69	40·0	69		Vomiting
18	5·642	69	40·0	92	S	Vomiting
Mean	58·650	83	39·8	67	Radical cure rate 100% (4/4)	
			Quinine and Clindamycin eight-hourly for three days at Half Dosage			
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)	
			Quinine eight-hourly for three Days			
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		Radical cure rate nil	

*Approximate median count.

†Where no symbol is shown final result could not be determined. RIII = No marked reduction of asexual parasitaemia. RII = Marked reduction of asexual parasitaemia but no clearance. RI = Clearance of asexual parasitaemia followed by recrudescence. S = Clearance of asexual parasitaemia without recrudescence (radical cure). (W.H.O., 1967.)

the parasitaemia was cleared and did not reappear on follow-up. These patients were judged to be radically cured. The average initial parasite count in these five patients ($33·269 \times 10^9$/l) was less than that ($73·511 \times 10^9$/l) 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.

Of the five patients whose initial infection was not controlled by clindamycin and who, because of a worsening clinical condition and parasitaemia, were given other treatment, two were cured by sequential therapy with quinine and Fansidar (pyrimethamine and sulfadoxine). Two other patients were cured by a single dose of Fansidar. The case history of one of these is given below. A clinical response to Fansidar occurred in the fifth patient but follow-up was not achieved. Thus the overall cure rate for clindamycin was 50%.

No clear-cut toxicity due to clindamycin occurred in these patients, though one (case 2) had persistent dizziness and weakness during treatment and tinnitus occurred for two days afterwards.

Case 12.—The patient was a 43-year-old farmer born locally. The main symptom was headache for four days. He had received two intramuscular injections (content unknown) the day before admission. He was distressed and had a fever of 40·0°C, though his parasitaemia was mild ($8·265 \times 10^9$/l). Clindamycin 450 mg was administered at 16.00 and 21.00 hours on the day of admission and thereafter at eight-hour intervals. The fever abated briefly next morning (day 1) but then returned to 40·0°C. The parasite count fell to $0·665 \times 10^9$/l on day 1 but then rose to $9·880 \times 10^9$/l on day 2. During the evening of day 2, because of the increased parasitaemia, the high fever (40·0°C), and persistent severe symptoms, drug failure (RII type) was diagnosed. Seven doses of clindamycin had been given. He then received a single dose of Fansidar (sulfadoxine 1·5 g and pyrimethamine 75 mg). The parasitaemia cleared within 48 hours and the fever within 60 hours. Blood films were negative on days 13, 21, and 30 and a radical cure was thus obtained.

QUININE AND CLINDAMYCIN AT FULL DOSAGE

Six patients (cases 13–18) were begun on treatment with quinine 540 mg base every eight hours and clindamycin 450 mg every eight hours given at the same time for three days (table I). The 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 one (case 13) the symptoms worsened during treatment but improved when the clindamycin was stopped. In case 15, despite a fall in the parasite count from 55·419 to $0·04 \times 10^9$/l severe anorexia developed after the sixth dose of clindamycin. Cases 16, 17, and 18 showed a similar clinical picture, the patients developing 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 caused no side effects when given alone.

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

QUININE AND CLINDAMYCIN AT HALF DOSAGE

Eight patients (cases 19–26) received combination therapy with half-dose quinine (270 mg) and approximately half-dose clindamycin (150 mg) every eight hours (table I). 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, three of whom were cured. A clinical response occurred in two others but follow-up was not achieved. The eighth patient (case 22) developed toxicity after four doses 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 below.

Case 19.—This patient received four full doses of quinine (three intravenously) without toxicity. He then received quinine and clindamycin at half dosage. After two doses he developed nausea, tightness in the chest, and severe retching which persisted for eight hours. The clindamycin was stopped. The symptoms improved though the quinine therapy was continued. After the nine-dose course had been completed the clindamycin was resumed until nine doses had been given. The patient had persistent weakness during that time. The parasitaemia and fever cleared but follow-up until day 28 was not achieved.

Case 20.—This patient received five full doses of quinine at eight-hour intervals uneventfully. Then the half-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 he felt listless. A radical cure was achieved.

Case 22.—This patient was virtually asymptomatic on admission, having mild headache and backache only. After two doses of quinine 540 mg and clindamycin 300 mg at 10.00 and 21.00 hours on the day of admission, he developed nausea and vomiting, headache, dizziness, and prostration. Next day he received quinine 270 mg and clindamycin 150 mg at 06.00 and 14.00 hours. He remained severely toxic with weakness and dizziness though the parasite count had fallen from 60 to $0·65 \times 10^9$/l. The clindamycin was stopped but the quinine was

continued and the dose increased to 540 mg; he improved and remained well. After 12 doses of quinine a single dose of Fansidar was given. The patient was cured.

QUININE ALONE

Three patients (cases 27–29) were treated with a three-day course of quinine alone. They developed recrudescences on days 14, 22, and 25 respectively (table I).

TETRACYCLINE ALONE

Four patients received tetracycline 250 mg every six hours for three days (table II). Two patients had an RIII response and one an RII response. A slow clearance of the parasitaemia occurred in the fourth patient but follow-up was not achieved.

TABLE II—*Therapeutic Results in Patients Treated with Clindamycin and Tetracycline**

	Duration of Therapy	Average Parasitaemia ($\times 10^9$/l)	Result			
			RIII	RII	RI	S
Patients treated with Clindamycin	3 Days	53·390	1	4		5
Patients treated with Tetracycline†	3 Days	20·647	2	1		

*Clinically clindamycin was more effective than tetracycline.

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

Discussion

Falciparum malaria in Thailand is difficult to eradicate in many patients. In recent studies the cure rates with chloroquine (Hall *et al.*, 1975 b) and pyrimethamine (Doberstyn *et al.*, 1975) were nil. Our results indicate that clindamycin is partially effective against chloroquine-resistant falciparum malaria in patients with clinically moderate disease. In some men the clinical response was rapid but in others it was slow or ephemeral. Our cure rate of 50% with multi-dose clindamycin contrasts with the 85% cure rate we obtained with a single dose of pyrimethamine and sulfadoxine (Doberstyn *et al.*, 1975). The average parasite clearance time for clindamycin (88 hours) was significantly longer ($P < 0{\cdot}05$) than that for pyrimethamine and sulfadoxine (71 hours). Wagner *et al.* (1968) found that clindamycin has a half life of only 2·38 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 (Brooks *et al.*, 1969). In our test system clindamycin was clearly a more powerful antimalarial than tetracycline (table II).

Clindamycin alone was not toxic in our patients. Nevertheless, several workers have shown that lincomycin and clindamycin (a chlorinated lincomycin analogue) can cause ulcerative colitis and even pseudomembranous colitis (Cohen *et al.*, 1973; Pittman *et al.*, 1974; Tedesco *et al.*, 1974). The diarrhoea usually begins after four to nine days of therapy. Colitis was not detected in our patients. Clindamycin is probably the most potent antimalarial among the antibiotics. Because of its partial efficacy and potential toxicity, however, 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. Miller *et al.* (1974), however, did not encounter gastrointestinal intolerance. In our patients retching and frank vomiting were commonly observed, whereas 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, all four patients followed up being cured. Possibly 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 after more conventional treatment—for example, 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—that is, the degree of "drug pressure" was increased. If only patients with counts over 50×10^9/l and uncomplicated disease are selected for drug trials comparative studies may be completed using fewer subjects. We have adopted this system without risk to the patients.

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