

Amodiaquine Resistant Falciparum Malaria in Thailand

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OBJECTIVE: To compare amodiaquine and chloroquine in the treatment of falciparum malaria in Thailand.

BACKGROUND: Interest in 4-aminoquinolines other than chloroquine was reawakened by Schmidt who found in owl monkeys that two chloroquine-resistant strains of *P. falciparum* were more susceptible to amodiaquine than to chloroquine. Rieckmann also reported the superiority of amodiaquine both *in vitro* and *in vivo* although radical cures were not achieved with amodiaquine in volunteers. Fitch demonstrated that owl monkey erythrocytes infected with chloroquine-resistant *P. falciparum* had a deficiency of chloroquine-¹⁴C uptake, but not a deficiency of amodiaquine-¹⁴C uptake. Therefore, we compared the therapeutic efficacy of the two drugs in an area endemic for chloroquine-resistant falciparum malaria.

DESCRIPTION: The study was performed at Trad Hospital in Southeast Thailand between March and July 1973. Chloroquine, given either orally or parenterally, is used frequently to treat patients with the clinical diagnosis of malaria; amodiaquine is not used at all. Chemoprophylaxis is not practiced in the community. All patients were fully informed of the nature of the drug trial and consent was granted voluntarily. They all had mild or moderate falciparum malaria with asexual parasitemias between 1,000 and 100,000 per cmm. Alternate patients were assigned to chloroquine or amodiaquine. The dosage form of chloroquine used was a non-enteric coated tablet ("Nivaquine", May and Baker, 150 mg of chloroquine base). The dosage form of amodiaquine was a non-enteric coated tablet ("Camoquine", Parke-Davis, 200 mg of base). The initial regimen was 1.5 g of the appropriate drug, administered over 3 days, 600 mg initially, 300 mg 6 hours later, and 300 mg on each of the succeeding 2 days.

Because only few patients were cured by 1.5g of amodiaquine given for 3 days, a 2.0g course for 4 days was studied in 9 additional selected patients with low parasitemias. Most patients received 400 mg (2 tablets) initially followed by 400 mg 6 hours later on day 0, then 400 mg on the morning of days 1, 2 and 3.

CHLOROQUINE 1.5 g:

In hospital, chloroquine cleared parasitemia in only 3 of 13 patients (Table 1). One of these patients developed a recrudescence during the 1 month follow-up period; the other two patients could not be traced and the responses are recorded as "RS" (parasitemia was cleared; thus RII or RIII were ruled out, but follow-up examinations were not achieved and the final result had to be either RI or S). In many patients chloroquine had little or no effect on parasitemia—a potentially dangerous situation. No patients were cured by chloroquine. Five of the treatment failures were next treated with amodiaquine 1.5g, and their subsequent responses were as follows: 1 patient was cured (S); 2 patients had recrudescence (RI); 1 patient responded only partly (RII) but did respond to a combination of sulfadoxine with pyrimethamine (S); and 1 patient could not be traced (RS response). The other 5 treatment failures were treated with other drugs but follow-up examinations were not obtained. Due to the obviously poor response to chloroquine, use of this drug was discontinued after 13 patients had been treated.

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AMODIAQUINE 1.5 g:

Amodiaquine was significantly ($p < 0.01$) more effective in clearing parasitemia (15 out of 17 patients) than chloroquine (Table 2). Four patients could not be followed-up (RS response); radical cures were achieved in 5 (38%) of the remainder.

The 8 patients who were not cured were then further treated as follows:

- 1) Five patients were treated with 3 tablets of Fansidar (sulfadoxine with pyrimethamine). One of these patients developed another recrudescence and the other 4 responded satisfactorily but did not return after discharge (RS response).
- 2) Two of the eight received quinine with an RS response.
- 3) One patient was cured by WR33063 (a 9-phenanthrene methanol under investigation).

Table 1. Falciparum Malaria in Southeast Thailand Treated with Chloroquine 1.5g over 3 Days

| Case Number | Age | Asexual Count <i>P. falciparum</i> (per cmm) | Parasite Clearance (Hours) | Initial Fever (°C) | Fever Clearance (Hours) | Result** | <i>P. vivax</i> after Discharge |
|-------------|-----|--|----------------------------------|-----------------------|-------------------------------|----------|---------------------------------------|
| 1 | 17 | 1820 | 68 | 37.7 | — | RS | |
| 3 | 21 | 3240 | N.C.*** | 37.7 | — | RII | |
| 5 | 17 | 12820 | N.C. | 39.5 | N.C. | RIII | |
| 7 | 26 | 1500 | N.C. | 38.8 | 74 | RII | |
| 9 | 57 | 6552 | N.C. | 39.0 | 51 | RII | |
| 11 | 20 | 18200 | 69 | 36.8 | — | RS | |
| 13 | 18 | 13160 | N.C. | 40.0 | N.C. | RIII | |
| 15 | 21 | 2340 | N.C. | 37.5 | — | RII | |
| 17 | 40 | 27391 | N.C. | 37.2 | — | RII | |
| 19 | 23 | 2710 | 41 | 39.0 | 63 | RI | |
| 21 | 25 | 21021 | N.C. | 38.8 | 52 | RII | |
| 23 | 43 | 49572 | N.C. | 38.5 | N.C. | RII | |
| 25 | 23 | 20637 | N.C. | 40.2 | N.C. | RII | |
| Average | 27 | 13920 | N/A | 38.5 | 60 | | |

* Fever clearance was computed only when the initial fever was at least 38° C.

** RIII, no marked reduction of asexual parasitemia; RII, marked reduction of asexual parasitemia but no clearance; RI, clearance, followed by recrudescence; S, Clearance without recrudescence. World Health Organization (1967) Chemotherapy of Malaria. WHO Tech. Rep. Ser. No. 375, p 42. We have added a suggested new symbol, namely; RS, clearance, but no follow-up examinations. (see text)

*** No clearance.

Table 2. *Falciparum* Malaria in Thailand Treated with Amodiaquine 1.5g over 3 Days

| Case Number | Age | Asexual Count <i>P. falciparum</i> (per cmm) | Parasite Clearance (Hours) | Initial Fever (°C) | Fever Clearance (Hours) | Result | <i>P. vivax</i> after Discharge |
|-------------|-----|--|-------------------------------|-----------------------|----------------------------|--------|---------------------------------------|
| 2 | 44 | 4320 | 66 | 37.7 | — | RS | Day 51 |
| 4 | 47 | 8730 | 90 | 37.5 | — | RI | |
| 6 | 27 | 12376 | 76 | 37.7 | — | RI | |
| 8 | 18 | 34830 | 60 | 39.5 | 46 | S | |
| 10 | 18 | 18425 | N.C. | 38.6 | 55 | RII | |
| 12 | 18 | 14256 | 93 | 39.5 | 19 | RS | |
| 14 | 30 | 7917 | 47 | 37.5 | — | S | |
| 16 | 34 | 9100 | 65 | 39.7 | 13 | RS | |
| 18 | 44 | 13190 | 117 | 39.0 | 79 | RI | |
| 20 | 37 | 21060 | 75 | 38.0 | 43 | RS | |
| 22 | 30 | 9100 | 48 | 37.6 | — | S | Day 44 |
| 24 | 49 | 7735 | 105 | 39.4 | 55 | RI | |
| 26 | 15 | 35900 | N.C. | 37.9 | — | RII | Day 45 |
| 27 | 29 | 54000 | 70 | 40.3 | 86 | S | |
| 28 | 17 | 20000 | 69 | 38.0 | 56 | RI | |
| 29 | 25 | 18428 | 70 | 37.3 | — | RI | |
| 30 | 18 | 18200 | 100 | 38.2 | 20 | S | |
| Average | 29 | 18092 | 76.7 | 38.4 | 47.2 | | |

Table 3. Falciparum Malaria in Southeast Thailand Treated with Amodiaquine 2.0g over 4 Days

| Case Number | Age | Asexual Count <i>P. falciparum</i> (per cmm) | Parasite Clearance (Hours) | Initial Fever (°C) | Fever Clearance (Hours) | Result | <i>P. vivax</i> after Discharge |
|-------------|-----|--|-------------------------------|-----------------------|----------------------------|--------|---------------------------------------|
| 31 | 38 | 7392 | 94 | 37.7 | — | S | Day 59 |
| 32 | 15 | 21140 | 75 | 39.8 | 43 | RS | |
| 33 | 41 | 2700 | 41 | 38.9 | 32 | S | |
| 34 | 17 | 3680 | 41 | 37.7 | — | RS | |
| 35 | 15 | 2916 | 67 | 40.0 | 42 | S | |
| 36 | 20 | 5265 | 43 | 37.2 | — | S | |
| 37 | 23 | 16562 | 115 | 39.4 | 18 | RI | |
| 38 | 29 | 9696 | 88 | 37.3 | — | RI | |
| 39 | 27 | 4050 | 63 | 39.6 | 14 | S | |
| Average | 25 | 8155 | 69.7 | 38.6 | 29.8 | | |

Table 4. Comparison of Cure Rates

| Drug | Mean Parasite Count (per cmm) | | | | | Total | Cure Rate |
|------------------|-------------------------------------|------|-----|----|---|-------|-----------|
| | | RIII | RII | RI | S | | |
| Chloroquine 1.5g | 14000 | 2 | 8 | 1 | 0 | 11 | 0% |
| Amodiaquine 1.5g | 18000 | 0 | 2 | 6 | 5 | 13 | 38% |
| Amodiaquine 2.0g | 8000 | 0 | 0 | 2 | 5 | 7 | 70% |

AMODIAQUINE 2.0 g:

The parasitemia was cleared in all 9 patients (Table 3). Two patients did not return for follow-up examinations; 1 of these patients had no parasitemia on days 14 and 24 but did not return on day 28 (RS responses). Two other patients returned only once, one on day 26, and one on day 30. They did not have detectable parasites in peripheral blood films and were considered radically cured. Two patients recrudesced on days 14 and 15 respectively. Over-all, 5 of 7 patients were adjudged to be radically cured by the 2.0g course. Since only patients with mild disease (average parasitemia 8,000) were treated, the over-all response was not considered favorable.

Urine specimens were obtained before treatment from 33 patients. Chromatography of these specimens showed spots corresponding to one or both of the 4-aminoquinolines in 29 of them. This indicated that a high proportion of the patients had received antimalarial drug therapy before admission. All 33 patients had evidence of 4-aminoquinolines in post-treatment urine specimens. The two drugs could not be reliably differentiated by the chromatography techniques employed.

Symptoms were frequently observed during chloroquine therapy and were at least partially attributable to the disease, which in most patients was not responding satisfactorily. Abdominal tightness, dizziness and other symptoms were fairly common in patients on amodiaquine therapy (although they were not more frequent than with chloroquine).

DISCUSSION: Falciparum malaria in Thailand responds poorly to chloroquine whether given as treatment or for suppressive prophylaxis. The logical deduction is that chloroquine should not be used for falciparum malaria in Thailand. In practice, chloroquine is frequently prescribed either orally or 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 resistance.

In accord with recent studies we found (Table 4) that amodiaquine was more effective (38% cure rate) than chloroquine (0%) in the treatment of chloroquine-resistant falciparum malaria. The predominant response was RI rather than RII; however, 38% is not a very impressive cure rate. The difference in cure rates may be partly explained by the fact that chloroquine is widely used in the community whereas amodiaquine is not used at all.

We do not recommend amodiaquine for the treatment of falciparum malaria in Thailand since both quinine and the combination of sulfadoxine and pyrimethamine (Fansidar) are more efficacious. Harinasuta (personal communication) recommends a short course of quinine (1-3 days) followed by a single dose of sulfadoxine with pyrimethamine as the preferred course of therapy.

SUMMARY: Amodiaquine cured 38% (5/13) of patients with falciparum malaria in Southeast Thailand. Chloroquine cured none (0/13). In hospital, amodiaquine cleared parasitemia significantly more frequently than did chloroquine, but neither drug was effective enough to warrant further use for falciparum malaria in Thailand. Insidious toxicity was observed with both drugs.

The responses of patients whose parasitemia was cleared in hospital but who did not attend for follow-up examination were recorded as RS (i.e. RI or S). This notation is presented as a suggested new addition to the W.H.O. classification.