QUININE-TETRACYCLINE FOR MULTIDRUG RESISTANT FALCIPARUM MALARIA

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Abstract. *Plasmodium falciparum* in Southeast Asia is highly resistant to chloroquine and sulfadoxine/pyrimethamine. Quinine-tetracycline has been used as a second line treatment for uncomplicated falciparum malaria, but duration of treatment varies from place to place. The 7-days course of this combination has been shown to be very effective. However, due to the cinchonism adverse effects, the patient compliance has not been satisfactory. We have evaluated the efficacy of a 7-days course of tetracycline in combination with either 5 or 7-days course of quinine.

Ninety male Thai patients who were admitted to the Bangkok Hospital for Tropical Diseases were randomized to receive tetracycline 250 mg *qid* for 7 days in combination with either quinine 600 mg *tid* for 5 days (Q5T7; group A) or quinine 600 mg *tid* for 7 days (Q7T7; group B). The patients were hospitalized for 28 days. Patients in both groups had a comparable initial response to treatment, with the clearance of fever and parasites within 4 days. There were 46 and 40 patients in group A and B, respectively, who completed the 28 day of follow-up. The cure rates were 87 and 100%, respectively for group A and B. No serious adverse effects were found in either group; transient nausea, vomiting and tinnitus were common findings. The incidence of adverse effects was not different between the two groups. The results from the present study suggest that a short course treatment of quinine (Q5T7) had significantly decreased the cure rate. In areas with quinine resistant falciparum malaria, a full course of 7-days quinine, in combination with 7-days course of tetracycline is recommended for hospital treatment. However, an alternative shorter course of antimalarials is suggested for home treatment.

INTRODUCTION

Plasmodium falciparum in Thailand is highly resistant to chloroquine and sulfadoxine/pyrimethamine and quinine resistant is increasing (Bunnag and Harinasuta, 1986; Harinasuta *et al*, 1990; Karbwang and Harinasuta, 1992). The combination of quinine and tetracycline has been used as second line drug treatment in many countries. The efficacy of 7-day quinine-tetracycline has been shown to be very effective (Karbwang *et al*, 1991; 1994; Looaree-suwan *et al*, 1992). However, due to the toxicity of quinine, the course of treatment of this drug regimen has been shorten to 3 or 5 days in the field condition. Nevertheless, there is no information on the efficacy of these shorter courses treatment of quinine. It has been recommended that the quinine concentration should be above the minimum inhibitory concentration (MIC) throughout 7 days (Chongsuphajaisiddhi *et al*, 1981). With quinine alone, inadequate quinine concentration from the fourth day of treatment onwards was reported to be responsible for the treatment failures (Chongsuphajaisiddhi *et al*, 1981; 1983; Karbwang *et al*, 1991); the lower quinine concentrations obtained is due to the faster quinine clearance during recovery from acute malaria infection (White *et al*, 1982).

We have compared the efficacy and toxicity of either a 5 or 7-days regimen of quinine in combination with 7-days course of tetracycline.

MATERIALS AND METHODS

Ninety patients with acute uncomplicated falciparum malaria (asexual form parasitemia of less then 5%), with no history of liver or kidney diseases who were admitted to the Bangkok Hospital for Tropical Diseases, Bangkok, during 1990-

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1992 were recruited into the study. The age was between 16 to 54 years and the weight was 40-81 kg. The hospitalization was 28 days. Written informed consent for participation to the study was obtained from all of the patients. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

The patients were randomly allocated to the following therapeutic regimens;

Group A: Quinine 600 mg *tid* for 5 days plus tetracycline 250 mg *qid* for 7 days (Q5T7)

Group B: Quinine 600 mg *tid* for 7 days plus tetracycline 250 mg *qid* for 7 days (Q7T7)

Patients who failed to respond to the treatment were retreated with regimen used for group B.

Parasite count was performed every 6 hours until negative then daily for 28 days. The microscopic identification of parasite was done on a thin/thick smear with Giemsa's stain, and parasite counts were reported per 1,000 RBCs or per 200 WBCs.

All adverse reactions during the study period were recorded with the date and time when they occurred and disappeared. The severity was graded into 4 degrees; 1 for normal, 2 for mild, 3 for moderate and 4 for severe. The changes included gastro-intestinal, central-nervous, cardiovascular, dermatological and other changes possibly attributable to quinine or tetracycline.

The patients were included for efficacy assessment if the follow-up period had been completed to day 28. The efficacy and adverse effects were compared between the two therapeutic regimens. The evaluated parameters were parasite clearance time (PCT: the time taken for the parasite count to fall below the level of microscopic detection), fever clearance time (FCT: the time taken for the temperature to return to normal *ie* below 37.3°C), cure rate and the occurrence of adverse effects. Statistical analysis was done by Fisher's exact test for proportion, or by the Mann-Whitney U-test for other variables, at statistical significance level of $p = 0.05$.

RESULTS

Ninety male patients with acute uncomplicated falciparum malaria were recruited into the study, 48 patients were in group A and 42 patients in group B. All of them presented with fever on admission. The levels of admission parasitemia were not statistically significantly different between the 2 treatment groups. The characteristics of the patients was comparable between the two groups (Table 1).

Four patients did not complete the 28 day evaluation period (2 in each group); the reasons of withdrawal were not associated with adverse effects. Loss of follow-up occurred on days 7 to 21. Only 86 patients were therefore qualified for the efficacy assessment.

Patients in either group had a similar initial response, median FCT and PCT for group A and B were 75 *vs* 75 hours, and 88 *vs* 90 hours, respectively. Reappearance of the parasitemia was found only in patients from group A (6 patients). In all cases, recrudescence occurred between days 22 and 28. The cure rates were 86.95% (95% CI = 77.2-96.7%) and 100% (95% CI = 100-100%), for group A and B, respectively (Table 2). The cure rates of the 2 groups were statistically significantly different ($p = 0.028$, RR 1.15, 95% CI = 1.03-1.29; Table 2).

Table 1

Admission clinical and laboratory data, presented as median and range.

	Q5T7	Q7T7
Age (years)	24 (17-40)	25 (16-54)
Weight (kg)	55.0 (42-75)	56 (40-81)
Temperature (°C)	38.5 (37.3-40.5)	39 (37.3-40.8)
Parasitemia (/μl)	23,424 (159-292,432)	24,542 (630-343,800)

Table 2

Therapeutic responses.

	Q5T7 (N = 48)	Q7T7 (N = 42)
FCT(h)	75	75
(median, range)	(4-136)	(12-132)
PCT (h)	88	90
(median, range)	(45-159)	(45-135)
Cure rate (%)	87	100
S response (N)	40	40
S/RI response (N)	2	2
RI response (N)	6	0
P. vivax (N)	3	3

Transient nausea, vomiting, dizziness, loss of appetite and tinnitus were the main complaint of the patients in either group. The occurrence of the adverse effects was not significantly different between the two groups.

Three patients from each group developed *P. vivax* malaria during the follow-up period.

DISCUSSION

There has been a decline in the sensitivity of *Plasmodium falciparum*, the cure rate for a 7-day course of quinine alone has been shown to be around 70-75% (Bunnag and Harinasuta, 1986). The result from the present study showed the parasite clearance time to be relatively slow *ie* median of 88 and 90 for group A and B, respectively. This may suggest the decline in its sensitivity (White, 1992). The FCT and PCT obtained from this study however are comparable to those reported earlier (Karbwang *et al*, 1991; 1994).

The initial response from both regimens was the same, with a comparable FCT and PCT. However, better cure rate was observed from regimen B. This may suggest that quinine on the last 2 days of treatment had an influence on the clearing of the remaining parasites. The results of the present study support the findings of Chongsuphajaisiddhi *et al* (1983) and Karbwang *et al* (1990) on the importance of maintaining quinine concentrations above the MIC throughout 7 days of treatment. Terminating quinine on day 5 is likely to produce a lower quinine concentrations on the last 2 days of treatment (*ie* days 6 and 7).

The regimen of quinine-tetracycline for 7 days (under supervision) has improved the cure rate to 100% (Karbwang *et al*, 1991; 1994, Looareesuwan *et al*, 1992). Under field conditions however, the cure rate is much lower *ie* 80%. This was claimed to be due to quinine toxicity which has led to poor patient compliance (Thimasarn - unpublished observation, 1993). Shortening the duration of quinine treatment did not seem to decrease significant adverse effects, but clinical efficacy (Table 2). In areas with decreased quinine sensitivity (evidenced by prolongation of FCT and PCT after quinine therapy), it is therefore suggested that the course of quinine treatment should be at least 7, rather than 5 days. This is of course more suitable for in-patients than out-patients. The patient compliance is expected to be poor with home treatment. It is recommended that alternative shorter course of antimalarials should be considered rather than shortening the course of quinine treatment, since the benefit is not seen, and the cure rate is significantly lower.

Vivax malaria was found in patients in either regimen. This suggests that either quinine or tetracycline has no effect on hypnozoite form of *P. vivax*. Primaquine is therefore essential for radical cure in vivax malaria.

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