FREQUENCY OF EARLY RISING PARASITEMIA IN FALCIPARUM MALARIA TREATED WITH ARTEMISININ DERIVATIVES

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Abstract. To define the frequency of the early rising of parasitemia in falciparum malaria patients treated with artemisinin derivatives, a retrospective chart review of 497 patients admitted to the Hospital for Tropical Diseases, Bangkok in 1996 was carried out. Early rising parasitemia, defined as an increase in the parasite count over the baseline pretreatment level during the first 24 hours of treatment, was found in 59/229 episodes (25.8%) of uncomplicated, and 111/268 episodes (41.3%) of complicated falciparum malaria. All uncomplicated cases were successfully treated without developing any complications. There were 2 deaths and 13 changes of drug regimen in the complicated group. Only one of these unfavorable responses was due to parasite response. Early rising parasitemia was very common in falciparum malaria treated with artemisinin derivatives, despite their ability to clear the parasitemia, and did not indicate failure of the drug used.

INTRODUCTION

An increase in blood parasite count in falciparum malaria patients after initiation of antimalarial treatment is not uncommon. There are very few reports addressing this phenomenon (Armitage and Blanton, 1991; Kramer *et al*, 1983; Gachot *et al*, 1996), and also its significance remains unclear. A retrospective study from France revealed that 14 out of 30 patients (42%) with severe imported malaria treated with quinine encountered early rise in parasitemia with subsequent reduction of the parasitemia without an aggressive therapeutic approach. (Gachot *et al*, 1996). In Thailand, falciparum malaria is considered multi-drug resistant (Looareesuwan *et al*, 1992a). Encountering this problem may cause physicians to think of drug resistance and lead to the decision to take a more aggressive treatment approach. Up to now, its impact on the patient's condition or the treatment outcome, *ie* survival in complicated malaria, or cure rate in uncomplicated malaria, are still unknown.

The objective of our study was to define the frequency of the early rise in parasitemia after initiation of artemisinin derivatives as antimalarial drugs, and to identify the magnitude and significance of the rise in patients with complicated and uncomplicated falciparum malaria who were treated in our hospital.

MATERIALS AND METHODS

The study was done by retrospectively examining the charts of the patients who were admitted to the Hospital for Tropical Diseases, Bangkok in 1996. Most of them had participated in clinical drug trials for antimalarial therapy or adjuvant therapy combined with standard antimalarial drugs. We included patients into the study if the diagnosis on admission was acute falciparum malaria (clinical and positive blood smear for the asexual stage of *P. falciparum*), if the patient had been treated with

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artemisinin derivatives, was aged 15 years or above, and was hospitalized until resolution of clinical symptoms and clearing of parasitemia was reached, unless death occurred. We excluded patients who participated in clinical trials to which access to the complete data record was prohibited by the original protocol, or where the complete medical record could not be retrieved by any reason. The illness was classified as complicated or uncomplicated malaria by World Health Organization criteria (Warrell *et al*, 1990). The drug regimen that was considered the best for severe falciparum malaria in our hospital was intravenous injection of artesunate 120 mg loading, followed by 60 mg every 12 hours until the total dose of 600 mg was reached (Looareesuwan, 1994). Mefloquine at 25 mg/kg, divided in two doses, was added after the last dose of artesunate in some patients, to achieve a higher cure rate.

From each medical record, we collected the demographic data, parasite count on admission, serial parasite count in the first 24 hours after start of treatment, and the drug regimen used.

The blood parasite count at the time of admission, before the start of the antimalarial drug, was considered the baseline parasitemia. Routinely after starting medication, parasite counts were done every 6 hours in case in complicated falciparum malaria and every 12 hours in uncomplicated malaria, until parasite clearance. Then, blood thick and thin film examinations were conducted daily until discharge. Asexual stages of *P. falciparum* were counted against 1,000 red blood cells in thin film or against 200 white blood cells in thick film. Then, in conjunction with blood cell count and white blood cell count, the parasite count could be calculated. The numbers were reported as asexual malaria parasites per 1 μl of blood.

For cases where any one of the parasite counts during the first 24 hours increased over the baseline level, the degree of increase was recorded using the highest proportion above the baseline (*eg* 1.5 times mean increase of parasite count, 50% over the baseline level). Since there were no data on the magnitude of increase that were considered significant, we categorized these values by using arbitrary cutoff levels of 1, 1.2, 1.5, 2.0 and 2.5 times.

The primary outcome of interest was the frequency of early rising parasitemia, which was defined as the increase in the parasite count over the baseline pretreatment level during the first 24 hours of treatment. Due to the physician's concerns about failure of treatment, the secondary outcome was unfavorable response to treatment. We defined unfavorable response to antimalarial treatment as (1) death directly related to malaria illness; (2) in patients initially treated with non-best drug regimens, the doctor's decision to change the regimen to the best for any reason; or (3) in patients who had been diagnosed with uncomplicated malaria on admission, the development of any conditions which defined complicated malaria. The data of complicated and uncomplicated cases were analyzed separately.

RESULTS

Study population

There were 673 cases of falciparum malaria admitted to the Bangkok Hospital for Tropical Diseases in 1996. One hundred and seventy-six were excluded due to unavailable or incomplete data. As a result, 497 medical charts were analyzed. Two hundred and sixty-eight were classified as complicated (or severe) falciparum malaria and 229 were considered uncomplicated on admission. A part of the clinical profiles of patients and trial results have been reported elsewhere (Wilairatan *et al*, 1998).

Patient characteristics and antimalarial treatments

The demographic data of patients are presented in Table 1. Most of them contracted malaria from the Thai-Myanmar border. Table 2 shows the antimalarial drug used in the first 24 hours. For complicated cases, their manifestations are shown in Table 3.

Table 1
Admitted falciparum malaria patient characteristics.

	Uncomplicated (229 cases)	Complicated (268 cases)
1. Age [Mean (SD)]	26.6 (10.2)	24.9 (9.1)
2. Sex (Male:Female)	156 : 75	147 : 121
3. Nationality [number (%)]		
Thai	53 (23.1)	37 (13.8)
Burmese	4 (1.7)	14 (5.2)
Mon	126 (55)	166 (61.9)
Karen	28 (12.2)	47 (17.5)
4. Parasitemia on presentation (parasite/μl)		
Geometric mean	11,217	88,912
Range	124-247,950	382-3,533,500
5. Fever clearance time (FCT; hours)		
Mean (SD)	34.3 (24.5)	64.6 (46.5)
6. Parasite clearance time (PCT; hours)		
Mean (SD)	50.1 (14.7)	54.5 (19.7)

Table 2
Antimalarial drug used during the first 24 hours.

Category	Number (%)
Uncomplicated	229 (100)
Artesunate 400 mg + Mefloquine 625 mg po	165 (72.1)
Artesunate 400 mg + Mefloquine 750 mg po	18 (7.8)
Dihydroartemisinin 200 mg po	46 (20.1)
Complicated	268 (100)
Artesunate 180 mg *iv* (Best)	139 (51.9)
Alternative regimens	129 (48.1)
Artesunate 120 mg *iv* followed by	
Rectal suppository 10 mg/kg	23 (8.6)
Rectal suppository 20 mg/kg	25 (9.3)
Artemether 3.2 mg/kg im	37 (13.8)
Artemether 4.8 mg/kg im	6 (2.2)
Arteether 3.2 mg/kg im	38 (14.2)

Frequency of early rising parasitemia

The frequency of increase in parasitemia, using various cutoff levels in both groups, is presented in Table 4.

Outcome of treatment with artemisinin derivatives

For uncomplicated falciparum malaria, all patients respond initially to the drug with resolution of the symptoms and clearing of the blood parasites. One hundred and seventy (74.2%) stayed in the hospital until recrudescence occurred

Table 3
Manifestation of complicated malaria.

Patients with	Number (%)
1. Prostration	156 (58.2)
2. Cerebral malaria	15 (5.6)
3. Renal failure	44 (16.4)
4. Pulmonary edema	6 (2.2)
5. Jaundice	93 (34.7)
6. Shock	4 (1.5)
7. Hyperparasitemia[a]	76 (28.4)
8. Schizontemia	130 (48.5)

[a]Parasite count ≥ 250,000/μl

Table 4
Early rising parasitemia.

Categories	Uncomplicated	Complicated
1. No rising	170 (74.2%)	157 (58.6%)
2. Rising < 1.2 times	3 (1.3%)	36 (13.4%)
3. Rising ≥ 1.2 times and < 1.5 times	13 (5.7%)	30 (11.2%)
4. Rising ≥ 1.5 times and < 2 times	13 (5.7%)	21 (7.8%)
5. Rising ≥ 2 times and < 2.5 times	10 (4.4%)	9 (3.4%)
6. Rising ≥ 2.5 times	20 (8.7%)[a]	15 (5.6%)[b]
Total	229 (100%)	268 (100%)

[a]Maximal rise 11.24 times
[b]Maximal rise 26.14 times

or completed the 28-day follow-up. Recrudescence occurred in 8 patients (4.7%).

For complicated falciparum malaria, 139 (51.9%) were treated with antimalarial regimens considered the best and 129 (48.1%) were treated with alternative regimens for complicated malaria under clinical trial. In the best regimen group, one patient died 73 hours after treatment (Table 5, Number 14). This patient encountered increased parasitemia, from 292,600/μl to 330,220/μl (1.13 times the initial count) at the 6th hour, then the parasites decreased and were cleared by the 48th hour. Despite clearance of the parasitemia, deterioration of clinical condition continued, *ie* acute renal failure, acidosis and shock, before death ensued.

For the non-best regimen treated complicated falciparum malaria, there were 13 patients for whom the treatment regimens were changed to the best regimens (5 by artemether and 8 by arteether initially). One patient died 17 hours after starting intramuscular arteether (Table 5, Number 13). This patient was admitted with cerebral malaria, acute renal failure, metabolic acidosis and hyperparasitemia. The study protocol was stopped 4 hours after starting due to clinical deterioration, progressive acidosis, renal failure and development of shock. Intravenous artesunate was given instead. The parasite count increased from 474,300/μl to 1,018,350/μl (1.42 times the initial count) on the 8th hour. Despite aggressive treatment, circulatory collapse did not respond to treatment and led to death. The last parasite count, done 3 hours before death, was still above the baseline (558,000/μl). Autopsies were not carried out for these two patients.

For another 12 patients, all were successfully treated with intravenous artesunate. The reasons for changing treatment were deterioration of clinical condition in 4 cases, rising of parasite count in 1 case and both clinical deterioration and rising parasite count in 7 cases. The median time for changing the drug was 20 hours (range 4-80 hours). Nine out of 12 of these changes were made within the first 24 hours. There was only one change that was based solely on the parasite count on the third day of treatment (Table 5, Number 9). This patient had early rising of the parasite count 3.16 times in the first 24 hours; after a significant reduction (>75%) at the 48th hour the parasite rose again at the 68th hour. His condition was good and he had only hyperparasitemia. The physician decided to change the drug regimen 80 hours after the start of the first medication (artemether). A summary of these 14 cases with unfavorable outcome of treatment is shown in Table 5.

All of the remaining 254 patients were successfully treated with initial drug regimens, with resolution of fever and clearing of blood parasite. This included 100 patients with early rising parasitemia. Complications were treated by supportive measures that were appropriate to their conditions, *eg* hemodialysis for acute renal failure or mechanical ventilation for patients with respiratory failure.

Of the patients who responded to treatment, 24 patients left the hospital after symptom resolution and parasite clearance, and another

Table 5
Summary of complicated falciparum malaria patients with unfavorable response to treatment.

No.	Age	Sex	Complication[a]	Treatment	Baseline parasitemia (μl)	Magnitude of rise (times)	Change of treatment	Time of change (hours)	Reason for change[b]	Outcome
1	25	M	CM, J	Artemether	345,800	1.38	Yes	22	C&P	Survival
2	20	M	CM, ARF	Arteether	27,300	26.14	Yes	20	C&P	Survival
3	33	M	CM, J, ARF	Artemether	1,229,310	1.38	Yes	8	C&P	Survival
4	40	F	J	Artemether	486,000	1.38	Yes	21	C&P	Survival
5	23	M	CM, J, ARF	Arteether	396,150	N	Yes	8	C	Survival
6	21	M	ARF	Artemether	730,800	1.18	Yes	20	C&P	Survival
7	37	F	CM, J	Artemether	562,320	N	Yes	5	C	Survival
8	23	F	ARF, J	Arteether	213,200	N	Yes	28	C	Survival
9	17	M	Hyp	Arteether	357,570	3.16	Yes	80	P	Survival
10	38	M	CM, ARF	Arteether	121,800	5.15	Yes	13	C&P	Survival
11	54	M	ARF, J	Arteether	482,160	2.27	Yes	28	C&P	Survival
12	25	F	CM, J, ARF	Arteether	69,460	1.78	Yes	4	C	Survival
13	24	F	CM, ARF, Ac	Arteether	474,300	1.42	Yes	4	C	Death
14	25	F	ARF, A, S	Artesunate	292,600	1.13	No	-	-	Death

[a]CM: Cerebral malaria, J: Severe jaundice, ARF: Acute renal failure, Hyp: Hyperparasitemia, A: Acidosis, S: Shock.
[b]C: Clinical deterioration, P: Parasite count increase.

230 completed the 28-day follow-up periods. There were 67 cases with recrudescence (29.1%). All recrudescences were successfully treated without developing any complications.

DISCUSSION

The frequency of early increase parasitemia after treatment with artemisinin derivatives was very common, despite their ability to clear the parasite from the blood (Jiang *et al,* 1982; Bunnang *et al,* 1991; Looareesuwan *et al,* 1992b). For patients with uncomplicated falciparum malaria, about one-fourth of the patients (25.8%) encountered this rise and all were successfully treated without developing any complications. Since these patients were rarely admitted to the hospital and no routine parasite count monitoring was done in usual clinical practice, this phenomenon often went unrecognized.

For patients with complicated falciparum malaria, a larger proportion (41.3%) encountered this rise. Most of these patients (100/111 or 90.1%) responded to the treatment given, except for a few cases of death or changes of treatment. Although the parasites were sensitive to the drug used, some patients with complicated falciparum malaria might deteriorate during the initial phase and finally respond to antimalarial and other supportive measures, but some succumbed. This potential for morbidity and mortality might cause physicians to consider more aggressive treatment, such as exchange transfusion or change of the antimalarial drug to higher potency. Both deaths in our study occurred in patients with multiple complications that were unresponsive to treatment, one with parasites cleared and the other with a parasite count still above the baseline. Another 12 cases, who initially received intramuscular artemether or arteether, were changed to intravenous artesunate. Most of these changes (9/12) were done in the early period when the complications were in continuing development and the decision for more aggressive therapy was made. There was only one change that was based solely on the parasite count on the third day of treatment.

Our study focused on unfavorable response to treatment because response and complications were the issues of management in this early period. We did not consider the cure rate, since it was affected by many factors in the later period, especially the total drugs that were used in the regimens that were widely different in our patients (Looareesuwan, 1994).

Classification of patients into uncomplicated and complicated falciparum malaria was made based on their condition on admission. Uncomplicated cases were treated with oral drug regimens, while complicated patients were treated with parenteral drugs. By intensive treatment of these defined complicated cases, the clinical courses that followed seemed to be benign in many of them.

Due to the lack of a definite cut point for determining significant parasite count rise, we first classified into arbitrary categories. Our data suggest that it might depend on the initial parasite count. Patients with uncomplicated malaria and low parasitemia may have a parasite increase over 10-fold without an adverse result, but in severe patients with hyperparasitemia, an increase in the 20% range might be associated with clinical deterioration and the drug trials were stopped.

Unlike other benign malaria, the peripheral blood parasite count in falciparum malaria reflects only the proportion that did not sequester (Silamut and White, 1993). The dynamic of parasitemia might depend on many factors, *ie,* multiplication, proportion of sequestered parasites and clearance host immune in addition to the killing effect of the antimalarial drug (Silamut and White, 1993; White *et al,* 1992). We did not study these factors in detail due to the retrospective nature of our study. In fact, we tried to address the phenomenon in the peripheral blood when it was evaluated serially. Different drug regimens were used for the treatment of falciparum malaria in our hospital during that time. These regimens might have different parasite clearance abilities. Artesunate given intravenously was considered the best because it was the most reliable route in these critically ill patients. For patients treated with these

drugs, we observed that many of them still had clinical progression or developing complications despite clearance of the parasite. Most complications could be treated supportively according to that organ system. Only the one patient who was unsuccessfully treated and finally died was reported as being unfavorable to treatment. A different situation occurred in clinical trials of alternative drugs in complicated malaria. The trial protocol included thresholds of clinical or parasitic deterioration, which led to the cessation of the study protocol and change to best regimen (rescue treatment). Other measures for reducing blood parasite load, such as exchange transfusion, were not used routinely in our hospital. Our results suggested that it is too early in the first 24 hours to evaluate parasite response to the drug used. Most of them had a favorable response when they were evaluated at 48 hours as the standard recommendation. We did not agree with previous reports that this rise in parasitemia was a good prognostic factor (Gachot *et al*, 1996) since most of our patients with unfavorable response to treatment experienced this phenomenon.

In conclusion, early rising parasitemia in the first 24 hours was very common in falciparum malaria that was treated with artemisinin derivatives. Most of them were successfully treated with initial regimens. Any changes in the antimalarial treatment in the first 24 hours should be guided by evaluation of the clinical course rather than parasite count in this very early period. However, rising parasitemia in only a small proportion of patients with hyperparasitemia should be carefully evaluated. This finding should not be applied to the drug other than artemisinin derivative, *eg* quinine, which has slower parasite clearance and greater drug resistance.

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