TREATMENT FAILURE OF FALCIPARUM MALARIA WITH FANSIDAR IN TAWAU SABAH, JANUARY – JUNE, 1982

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SUMMARY

One hundred and ten consecutive patients with falciparum malaria were treated with Fansidar and primaquine. Of the 61 patients who were followed up at one week, 4 (6.5%) failed to clear their parasitemia (1 R III and 3 R II treatment failures). Of the subsequent 40 patients who were seen again at one month, another 3 (7.5%) had recrudesced (R I treatment failure). A total of 7 patients thus experienced some form of treatment failure in the cohort of 40 who completed the one month follow up. Only 1 of these 7 patients (with R III treatment) failure) failed to respond to repeat Fansidar treatment, and may be the only one with true Fansidar resistance. The overall treatment failure rate of 17.5% (95% confidence interval: 6-29%) in the cohort who completed the study is consistent with the known clinical efficacy of Fansidar. These results suggest no significant Fansidar resistance in falciparum malaria found in Sabah.

INTRODUCTION

In the late seventies, clinical observers noted that falciparum malaria in Sabah was increasingly resistant to chloroquine treatment. [1]

In July 1978 to October 1979, an *in vitro* survey using the method developed by Rieckmann [2] of 89 hospitalised patients with *P. falciparum* malaria in 8 of the 23 districts in Sabah revealed 87% resistance of the parasite to chloroquine. [3]

Consequently, the Department of Medical Services of Sabah decided to switch to the use of Fansidar* in the primary treatment of falciparum malaria. [4]

Increasing incidence of treatment failure to Fansidar had been reported from Bangkok and south-eastern Thailand where Fansidar had been in use since the mid-seventies for primary treatment. [5,6,7] Recently, case reports of Fansidar treatment failure in Malaysia had also appeared. [8,9]

Noting this with concern, we decided to monitor the incidence of treatment failure to Fansidar in patients with falciparum malaria since the drug was adopted for primary treatment here 3 years ago.

METHODS

Eligibility

All consecutive clinic and ward patients with a diagnosis of *P. falciparum* at Tawau Hospital, Sabah in the period January to June, 1982 were studied.

Diagnosis

All febrile patients presenting to Tawau Hospital had blood films taken and examined for malaria. *P. falciparum* was diagnosed on thick blood films. Infection was excluded after examining 150 microscopic fields. Only asexual forms were considered for inclusion in this study. Parasite density was scored as follows, using a table modified from Bruce-Chwatt: [10]

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* *Fansidar (Roche): sulfadoxine 500 mg + pyrimethamine 25 mg.*

Questionnaire

Upon diagnosis and after examination by a doctor, each patient was examined and quesioned by a malaria field worker or laboratory technician using a standardized questionnaire to elicit the following information:

Patient profile in terms of age, sex, race, work place and residence (in or outside Tawau, using city limits).
Probable immune status, indirectly assessed by the presence of a palpable spleen and a history of previous malaria infection (since the tests for malaria antibodies were not available).
Source of infection, ruling out imported infection by determining the history of recent travel outside the state within six months.
Severity of illness, by determining the duration of illness before diagnosis and the initial density of parasitemia at diagnosis.
Antecedent use of anti-malarial drugs.

A methemoglobin reduction test was done on all patients to determine the erythrocytic glucose-6-phosphate dehydrogenase (G6PD) activity.

Initial treatment

Single dose treatment with prepackaged Fansidar tablets (sulfadoxine 500mg + pyrimethamine 25mg) and primaquine tablets (7.5mg) as a gametocytocidal agent was given by a nurse according to the following schedule:

	AGE (yrs.)				
DRUG:	< 1	1-4	5-9	10-14	15 +
Fansidar tablet	1/4	1/2	1	2	3
Primaquine tablet	1	1 + 1/2	3	4	6

The patients were observed and the medications were repeated if vomiting occurred within one hour of drug administration. Patients were treated as outpatients unless their clinical condition warranted hospital admission. The determination of serum drug levels was not carried out because of logistical problems

Follow up and further treatment

The patients were reviewed one week and one month after initial treatment. Patients were considered cured if no persistence or reappearance of asexual forms of falciparum malaria was detected at the end of 28 days. Treatment failure was classified as follows, using criteria modified from those used in evaluating chloroquine resistance: [11]

TREATMENT FAILURE	PARASITEMIA AT ONE WEEK	PARASITEMIA IN THE PERIOD BETWEEN ONE WEEK TO ONE MONTH FOLLOWING DIAGNOSIS
R I	Cleared	Recrudesced
R II	Diminished	--
R III	Unchanged or increased	--

Patients who experienced initial R I and R II treatment failure were treated using the initial drug schedule and then followed up for a further one month to complete the study.

Patients who failed retreatment with either a persistence or recrudescence of parasitemia were to be treated with oral quinine (30mg/kg/day in 3 divided doses) and tetracycline (250mg QID) for one week. A further follow up of one month was to be completed.

Patients with R III treatment failure were to be treated with oral quinine and tetracycline straight away and followed up for one month.

The following exceptions to the treatment protocol were observed:

1. Patients with initial changes in mental status (drowsiness, obtundation, and coma) were treated as cerebral malaria with intravenous quinine (10mg/kg every 12 hours) till improved, followed by oral quinine (10mg/kg every 8 hours) for a total of 14 days. These patients were excluded from analysis.

2. Pregnant patients had primaquine and tetracycline omitted.

3. Patients with haemolysis (by history or examination) had primaquine omitted.

Statistical analysis

Statistical analysis of the patient characteristics was performed using chi-square and analysis of variance.

RESULTS

Compliance

One hundred and thirteen patients were diagnosed as having falciparum malaria at Tawau Hospital, Sabah in the period, January to June,

TABLE I
ANALYSIS OF COMPLIANT AND DEFAULTED PATIENTS

CHARACTERISTICS	PATIENTS WHO COMPLETED ONE WEEK FOLLOW UP n = 61 (%)	PATIENTS WHO COMPLETED ONE MONTH FOLLOW UP n = 40 (%)	PATIENTS WHO DEFAULTED ALL FOLLOW UP n = 49 (%)	p value*
1. Sex:				
Male:	48 (78.7)	32 (80.0)	42 (85.7)	
Female	13 (21.3)	8 (20.0)	7 (14.3)	N.S.
2. Age, in years: (mean ± S.D.)	19.1 ± 13.1	18.8 ± 13.6	21.2 ± 10.9	N.S.
3. Race:				
Bugis	20 (33.9)	13 (32.5)	20 (40.8)	N.S.
Suluk	2 (3.4)	2 (5.0)	5 (10.2)	N.S.
Chinese	6 (10.2)	4 (10.0)	1 (2.0)	N.S.
Bajau	5 (8.5)	4 (10.0)	4 (8.2)	
Kadazan	3 (5.1)	3 (7.5)	3 (6.1)	
Murut	4 (6.8)	0 (0.0)	0 (0.0)	
Others: **	19 (32.2)	14 (35.0)	16 (32.7)	
4. Residence Outside Tawau:	35 (58.3)**	23 (59.0)**	31 (63.3)**	N.S.
5. Past history of malaria:	23 (37.7)	15 (37.5)	15 (30.6)	N.S.
Splenomegaly:	11 (18.0)	5 (12.5)	10 (20.4)	N.S.
Recent foreign travel within 6 months:	2 (3.2)	1 (2.5)	4 (8.1)	N.S.
6. Duration of illness, days:	3.5 ± 2.2 (a)	3.3 ± 2.1 (b)	3.9 ± 3.1 (c)	N.S.
7. Antecedent use of anti-malaria drugs for the present illness:				
Chloroquine:	9 (14.8)	2 (5.0)	9 (18.4)	
Fansidar:	11 (18.0)	8 (20.0)	9 (18.4)	N.S.
Primaquine:	10 (16.4)	8 (20.0)	8 (16.3)	
8. Initial parasitemia: (score range: 1+ to 4+)	1.8 ± 0.9	1.9 ± 0.9	2.2 ± 1.0	N.S.

* Statistical test of significance for all three columns
N.S. = not significant at the 5% level
** unavailable for 1 patient
(a), (b), (c): excludes 2 patients with more than 30 days of illness in each group, (a): excludes 5 patients, (b) excludes 1 patient, and (c) excludes 6 patients with illness of uncertain duration.

1982. One died a week after diagnosis of chronic uremic encephalopathy due to obstructive uropathy. Two patients had cerebral malaria. These 3 patients were not included in the analysis.

Of the remaining 110 patients, 61 (55.5%) had a repeat blood film examined at one week.

Of these 61 patients, 40 (36.4%) completed the one month follow up required in the study. All these patients remained at home and returned to the hospital for their periodic examination.

Patient profile

Of the 61 patients who completed one week follow up (see Table I), four-fifths were male, around twenty years old, and a third of them were Bugis. Over half of them were living and working in plantations and timber camps outside Tawau. The 40 patients who went on to complete the one month follow up were similar in all these aspects.

Only 38% had malaria previously and only 18% had a palpable spleen on admission, suggesting that

we are dealing with a fairly susceptible population having malaria for the first time.

Very few (3%) had travelled outside the state within six months, thus reducing the probability of imported malaria.

The mean duration of illness was short, viz. 3.5 days, except for two patients who complained of illness for a period of more than one month before diagnosis.

Again, there were no significant differences in these respects between those who completed the one week and one month follow up (see Table I).

Eleven patients had used Fansidar on their own for the acute illness before diagnosis, and 10 of them responded to the treatment protocol under supervision. Only 1 patient who had used Fansidar and primaquine for his acute illness before diagnosis experienced R III treatment failure, and did not respond to retreatment with the same drugs.

The mean initial parasitemia, on a scoring scale of 1+ to 4+, was 1.8+, suggesting low parasite density (in the region of 2000 parasites per cu. mm).

Defaulters

The 49 patients (44.5%) who defaulted all follow up were analysed as shown in Table I. In regard to the variables measured, they were not significantly different from those who completed the study. However, the defaulters tended to be foreign migrant male workers from the more inaccessible jungle areas presenting with slightly heavier infections.

Treatment Failure

One patient experienced R III treatment failure with unchanged parasitemia at the end of one week. Three out of 61 patients failed to clear their parasitemia one week after initial treatment, and thus were classified as R II treatment failures.

Of the 40 patients who were examined at one week and again at one month after initial treatment, 33 had achieved radical cure. 4 had failed to clear their parasitemia at one week (the same 4 counted above) and another 3 developed recrudescence in the period between one week and one month of follow up, giving a total treatment failure rate of 17.5% for this group. The 95% confidence interval for this rate is between 6 to 29%.

Since the 3 patients with recrudescence had returned to endemic malarial areas, some of these recrudescences may in fact represent reinfections. The overall treatment failure rate may be an over-estimate.

Other Clinical Outcome

All the patients with R I and R II treatment failure responded successfully to a second course of Fansidar (see Table II). The one patient with R III treatment failure was unfortunately not treated according to protocol. He was inadvertently treated with Fansidar and primaquine again (when in fact quinine and tetracycline were indicated), and failed to clear his parasitemia one week later. Interestingly, chloroquine and proguanil were administered (again out of protocol), with clinical cure! He remained parasite-free on follow up 28 days later.

No patient complained of any serious untoward effects from the treatment regime. Four patients had complete G6PD deficiency, but experienced no hemolysis on treatment.

DISCUSSION

Tawau is a town on the south-eastern corner of the state of Sabah adjacent to the border with Indonesian Kalimantan. Of the population of 122,000 in the district of Tawau in 1980, [12] at least 20% was estimated to consist of migrant Indonesian workers employed in the cocoa and oil-palm plantations and timber camps. These workers working in and near newly cleared jungle were especially vulnerable to malaria infections. [13]

ENDEMICITY

Malaria is endemic in Tawau district, especially in the timber camps and newly established plantations. In 1982, the local Malaria Office reported a total of 1470 malaria cases, of which 40% were in migrant workers. As shown in this study, most of the malaria cases were contracted locally.

TREATMENT FAILURE

Clinical reports in the early seventies noted the presence of chloroquine resistance in *P. falciparum* infection around Tawau. [1]

In 1973, a strain of *P. falciparum* was isolated

TABLE II

DETAILS OF PATIENTS WHO FAILED TO RESPOND TO FANSIDAR

R	Age Sex yrs	Duration of illness in days	Initial parasitemia at Day 0	Parasitemia at Day 7 ± 1	Follow up period (from Day 0) before recurrence	Density of parasitemia	Further follow up period (days) free of parasite
III	17 M	>30	+	+ **	16 ***	+	28
II	29 M	3	+ +	+ **	0	0	28
	6 M	1	+ +	+ **	0	0	30
	17 M	1	+ +	+ **	0	0	30
I	23 F	7	+ +	NA	12 **	+ +	14
	22 F	2	+ +	NA	14 **	+ +	28
	5 M	7	+ +	0	26 **	+	7

** Treated with Fansidar and primaquine as described in the protocol

*** Treated with chloroquine and proguanil, out of protocol

R = Type of treatment failure, Sex: M = male, F = female, Duration of illness in days before diagnosis, Follow up period in days (from Day 0) before recurrence of parasitemia, Density of parasitemia at the time of recurrence

NA = not available, 0 = absent

from a patient in Beaufort which exhibited *in vitro* resistance to chloroquine. [14]

In 1978, an initial epidemiological survey to assess this problem of drug resistance was attempted. *In vitro* testing of 20 *P. falciparum* strains at Keningau showed a chloroquine resistance rate of 75%. [3]

Further *in vitro* testing from July 1978 to October 1979 of another 89 cases yielded a chloroquine resistance rate of 38.6%. [3] These cases were mainly collected on the west coast, except for 12 cases from Tawau on the east coast of which 11 were resistant.

These field surveys suffered from several weaknesses:

1. Case selection was unspecified. It is not clear whether these cases represented a population at higher risk for chloroquine-resistant *P. falciparum*.

2. Because of technical problems, these 89 cases represented only 61% of the actual number of cases tested.

Another one may conclude that chloroquine resistance existed in Sabah in 1978, the extent and degree of resistance were not firmly established.

Subsequent *in vitro* testing continued into 1981 giving a cumulative total of 211 cases over the period 1978-81. 135 tests (64%) were successful of which 109 (81%) were resistant. [15] This study is also subject to similar criticisms cited above.

In any case, in June 1979, the Malaria Control Programme in Sabah switched from the use of chloroquine to Fansidar in the treatment of uncomplicated falciparum malaria. The introduction of Fansidar as the primary medical treatment for falciparum malaria was made not without misgivings. Thailand had been using Fansidar extensively in the treatment of falciparum malaria since the mid-seventies. One series from Bangkok [5] showed an increase of treatment failure with Fansidar from a rate of 15-18% in 1975-76 to 48% by 1977-78. In 1982, another report from the Thai-Khmer border [6] showed complete failure of Fansidar to eradicate falciparum malaria contracted by Thai soldiers who had been on continuous Fansidar prophylaxis. This alarming trend confirms the fear that the continuous use of single drug treatment for prophylaxis and treatment will yield drug resistance. [7]

Case reports of treatment failure to Fansidar in Malaysia had recently appeared. Three children from an aboriginal family failed to respond to Fansidar despite repeated treatment. [8] A Vietnamese refugee with falciparum malaria probably acquired in Mersing, Johor, had R III treatment failure to Fansidar despite adequate drug absorption and elimination. [9]

However, not all treatment failures with Fansidar are necessarily due to plasmodial drug resistance. The clinical efficacy of Fansidar has not been 100%. A treatment failure rate of 15-20% with Fansidar in field conditions had been observed in several series. [16,17,18] Individual host factors may be important; for example, failure of absorption or rapid metabolism of the drug. However, acetylator

phenotype had not been shown to be important. [19,20] Even with adequate serum and erythrocytic drug levels, treatment failure had been documented in one case of drug-sensitive falciparum infection. [21] Other undetermined host erythrocytic factors must be responsible.

No *in vitro* test for Fansidar-resistant Plasmodium is yet available to confirm the presumptive clinical suspicion of drug resistance as has been the case with chloroquine resistance. Thus, in lieu of such *in vitro* confirmatory testing, a program of periodic clinical sampling as in this study to monitor the treatment failure rate to Fansidar would provide an indirect measure of the trend of Fansidar resistance in *P. falciparum*.

The finding of 17.5% treatment failure in patients with falciparum malaria diagnosed at Tawau Hospital in 1982, three years after extensive use of Fansidar, is consistent with previously published results of the expected treatment failure rate with Fansidar and does not suggest significant drug resistance.

Furthermore, of interest is the fact that of the 7 patients with initial treatment failure, 6 responded to retreatement. This could be attributed to various factors like lower parasitemia at the time of retreatment; delayed drug absorption with initially low serum concentration, rapid drug metabolism or partial drug resistance which was overcome by higher drug levels after retreatment (since the half-life of sulfadoxine is 168 hours). Thus only 1 patient with falciparum malaria in this study may have true Fansidar resistance.

This study suffered a serious weakness in that of the original 110 consecutive patients diagnosed of falciparum malaria, up to 45% defaulted all follow up. It cannot be determined whether they were more or less likely to harbour Fansidar-resistant malaria. However, it seems that the patients defaulted follow up because of socio-geographical reasons rather than for reason of their illness.

Perhaps the patients who came to the hospital for treatment of malaria had more "resistant" illness than those who visited the camp clinics, health centres and general practitioners in the community. However, this could not be ascertained from the study.

We have shown that only 18% acknowledged having taken Fansidar on their own before coming to the hospital, and most of them responded to supervised treatment. The antecedent use of Fansidar did not necessarily predispose to treatment failure.

CONCLUSION

Despite the uncertainties inherent in this kind of field study, the treatment failure rate of 17.5% remains a reasonable baseline estimate for future comparisons in similar clinical trials.

As it will take time for drug-resistant malaria to spread, a program of periodic monitoring of the rate of clinical treatment failure would provide a practical method for detecting the appearance of drug resistance.

In particular, since this study had established a baseline level of treatment failure of Fansidar treated falciparum malaria in Tawau Hospital, Sabah, further periodic monitoring at Tawau should be established as part of the routine services of the local Malaria Office there towards this purpose.

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