

Investigation of Possible Quinine and Fansidar
Resistant Cases of *Falciparum* Malaria
in a Refugee Camp

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OBJECTIVE : To investigate the reported occurrence of R₃ Quinine and Fansidar resistant cases of *P. falciparum* malaria in a Cambodian Refugee Camp.

BACKGROUND : During the late rainy season of 1978, it was the impression of the resident physician at the Aranyaprattet Refugee Camp (and was agreed to by physicians at other refugee camps) that R₃ level Quinine and Fansidar (sul-fadoxine 500 mg and pyrimethamine 25 mg) resistant cases of *falciparum* malaria were occurring among his patients.

Usual therapy for malaria at the Camp, regardless of type, consisted of three tablets of Fansidar and oral quinine to be taken for six days. If oral medication could not be tolerated, intramuscular Fansidar and intravenous quinine was used until such time as oral medication could be substituted (1). Both oral and parenteral therapy regimens have been shown to be effective, although parenteral administration is perhaps slightly less satisfactory than the oral regimen (2, 3).

The Camp maintained a prophylaxis program consisting of either three tablets of Fansidar given at one time at monthly intervals or one tablet every week for especially vulnerable personnel (approximately 300). These regimens have been shown to be over 85% effective in well-controlled trials (4, 5).

METHODS : Records on those patients seen prior to arrival of the AFRIMS team who had been treated with the above regimens and subsequently developed a positive malaria smear within one month were reviewed ("old patients").

Malaria slides were prepared on all new cases of possible malaria during a two week period using Giemsa stain (a total of 89 cases) and the corresponding Fields' stain slides, prepared by the Camp's technicians, were examined in 71 of these cases ("new patients"). In addition, slides of ten old patient cases, read as positive for malaria by the Camp technicians were examined. All slides were read independently by three experienced technicians in the Department of Epidemiology, AFRIMS. An examination for 30 minutes was required before a slide was declared negative. In the event of disagreement between the readers (2 cases) the slide was examined by the Chief, Department of Epidemiology,

RESULTS : Thirteen old patient cases were studied. These had occurred over the previous four months; Fansidar and/or quinine achieved less than optimal results in all of them. During July through October 1978, 563 cases of malaria were diagnosed at the Camp (89.7% *P. falciparum*) with the vast majority (at least

90%) receiving oral therapy on an outpatient basis, but specific quantitation of numbers of patients receiving oral or parenteral therapy was not possible.

Discussion of old patient cases will be divided into responses to the three regimens described above, namely oral therapy, parenteral therapy and chemoprophylaxis (Case reports). With the exception of one case of cerebral malaria, all of these cases eventually resolved on Fansidar and quinine therapy. Where additional drugs were used, they are also noted.

Five patients maintained parasitemias for prolonged periods after oral Fansidar therapy. This period lasted 3, 5, 6, 6 and 22 days in cases 1-5 respectively. The first three of these were hospitalized for the entire period. The fifth case was treated as an outpatient and no smears were obtained between days 1 and 22. One case lasting 6 days occurred during the study period and the patient was admitted, but not for malaria. Camp laboratory technicians reported positive malaria smears on days 2 and 7. Smears taken on days 2 and 3 by our technicians were negative.

In regard to parenteral therapy, five patients did not respond favorably. One case (6) succumbed to cerebral malaria 48 hrs. after admission. Case 7, after apparent recovery from falciparum malaria, required retreatment 18 days after treatment with three vials (mg equivalent to three tablets) of Fansidar IM, intravenous quinine for four days and oral quinine for three additional days. Oral Fansidar and quinine at that time did not prevent convulsions presumably due to cerebral malaria, but the patient recovered on supportive care and IV quinine. Cases 8 and 9 maintained parasitemias 6 and 7 days respectively after initiation of therapy and case 10 represents a mixed vivax and falciparum infection with recrudescence of both types 13 days after parenteral Fansidar.

Case 11 and 12 represent failures of weekly prophylaxis and case 13 represents failure of the monthly regimen.

Assuming that all of the "old patient" smears had been read correctly, (in only one case do we have information that directly bears on these cases), cases 1-4, 8, 9 and 11-13 do not meet WHO criteria for designation of resistance (6). Case 5 may be R₁ resistance or reinfection, but cases 7 and 10 are clearly R₁ recrudescences. Case 6 (and possibly case 7) would be termed R₃. The record is not clear at what point in the progression to coma, treatment with Fansidar was initiated, but early failure of thereapy was evident. Three chemoprophylaxis failures in approximately 1200 person-months is comparable to that found in the clinical trials (7) and is probably close to an operational minimum for a prophylaxis program.

Seventy-one Camp prepared and read blood films (Fields' stain), taken from new patients, were available for comparison with Giemsa stained slides prepared and read by AFRIMS technicians. Of these 71 slides, the Camp technicians read 10 as positive (nine *P. falciparum* and one *P. vivax*). Of the comparable Giemsa stained slides only two were read as positive. Examination of the Fields' stained slides by Institute technicians resulted is only the same two individuals being diagnosed as malaria (both falciparum). In two cases where the Fields' stained slide was unavailable, but the Giemsa stain

was positive, the Camp technician also called the case positive. In one case *P. vivax* was found in a Giemsa stained slide that was read as negative on the Fields' stain both by the Camp technicians and technicians of the Institute,

Therefore, a 67% false positive rate (8/12) and an approximately 1% false negative rate (1/77, 61 of these Fields' stain confirmed by the Institute) was determined. The one false negative slide was due to staining technique rather than reader error. (In addition, five of the Camp's ten "positive reference" slide sets were read as negative).

This study has been terminated.

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CASE REPORTS

Case Histories - Aranyapratet Refugee Camp
(Day 1 will always be date of presentation to hospital)

1. Case 600/21 23 year old male.

: Smear : *P. falciparum*
Treatment : Fansidar (iii tab)
Quinine (IV x 2 days)

Smear : *P. falciparum*
Treatment : Quinine (IV x 1 day, po x 4 days)

Day 4 : Afebrile

2. Case 2339/19 33 year old male.

The patient worked in the forest for 10 days prior to presentation.

Day 1 : Smear : *P. falciparum*
Treatment : Fansidar (iii tab)
Quinine (IV x 5 days)

Day 3 : Drop in temperature.
Smear : *P. falciparum*
Treatment : Bactrim (po x 5 days)

Day 4 : Smear : *P. falciparum*

Day 5 : Afebrile
Smear : *P. falciparum*
Treatment : Quinine (po x 3 days)

3. Case 858/21 68 year old.

Day 1 : Febrile
Smear : negative
Treatment : Fansidar (iii tab)

Day 6 : Febrile
Smear : *P. falciparum*

4. Case 1895/21 17 year old male.

The patient was admitted for anthrax of the lip and (R) cheek.

Day 2 : Febrile

Smear : *P. falciparum*

Treatment : Fansidar (iii tab)
Quinine (IV x 4 days)
Ampicillin
Kanamycin

Day 5, 6 : Afebrile

Day 7 : Febrile

Smear : *P. falciparum*

5. Case 1410/21 15 year old.

1 : Smear : *P. falciparum*

Treatment : Fansidar (iii tab)
Quinine (IV x 2 days)

Day 22 : Smear : *P. falciparum*

Treatment : Fansidar (ii tab)

6. Case 2711/19 41 year old Chinese female. The patient had not left the Camp for three years. She had no past history of malaria

Day 1 : Vertigo and headache progressing to deep coma within 18 hours.

Afebrile

Smear : negative

Treatment : Quinine (IV)
Fansidar (1M)

2 : Febrile

Smear : negative

Transfer to Aranyapratet Hospital

Smear : *P. falciparum*

Day 3 : Died (dx : cerebral malaria)

7 Case 1767/21 26 year old male.

Hospitalized

Smear : *P. falciparum*

Treatment : Fansidar(3 vials IM)
Quinine (IV x 4 days)
Quinine (po x 3 days)

Day 11 : Discharged

Day 18 : Complaint of headache and fever

Smear : *P. falciparum*

Treatment : Fansidar (ii tab)
Quinine (po)

Day 22 : Convulsions requiring hospitalization

Smear : *P. falciparum*

Treatment : Quinine (IV)
Valium (IV)

8. Case 1278/21 21 year old male.

The patient worked in the forest for one month prior to presentation.

Day 1 : Smear : *P. falciparum*

Treatment : Fansidar (1M)
Quinine (IV x 1 day, po x 1 day,
IV x 2 days, po x 1 day,
IV x 1 day)

Day 4, 5 : Smear : *P. falciparum*

Treatment : Procaine penicillin (po x 8 days)

: Smear : *P. falciparum*
became afebrile

Day 7 : Smear : Negative

Constitutional symptoms unresolved.

Day 9 : Treatment : Bactrim (po x 5 days)

Day 11 : Treatment : Quinine (IV x 1 day)

Patient discharged.

9. Case 1218/21 25 year old male.

Day 1 : Smear : *P. falciparum*
Treatment : Fansidar (1M)
Quinine (IV x 4 days, po x 2 days)

Day 3 : Smear : *P. falciparum*
Treatment : Procaine penicillin (1M x 3 days)

Day 5, 6, 7 : Smear : *P. falciparum*

Day 9 : Afebrile

10. Case 656/19 12 year old male.

Day 1 : Hepatomegaly and jaundice

Day 3 : Smear : *P. falciparum* and *P. vivax*

Day 4 : Treatment : Fansidar (1M)
Quinine (IV x 6 days)
Tetracycline (po x 11 days)
Smear : Negative

Day 7 : Afebrile

Day 11 : Jaundice resolved; patient discharged.

Day 17 : Readmit : Fever, convulsions.

Smear : *P. falciparum* and *P. vivax*
Treatment : Fansidar (1M)
Quinine (IV x 4 days, po x 5 days)
Chloroquine (450 mg x 4 days)
Prednisolone (20 mg x 6 days)

Day 19 : Smear : *P. vivax*

Day 20 : Smear : *P. falciparum*

Day 21 : Afebrile

Day 23 : Smear : Negative

Case 1752/21 25 year old male.

The patient was on Fansidar prophylaxis (i tab q week)

Day 1 : Symptoms of chills and nausea

Smear : Negative

Treatment : Fansidar (iii tab)
Quinine (po x 1 day)

Day 3 : Smear : *P. falciparum*
Treatment : Quinine (po x 4 days)

Day 6 : Smear : Negative

Note : Patient was never febrile.

Case 1107/20 25 year old male.

The patient was on Fansidar prophylaxis for approximately 6 months (i tab q week)

Day 1 : Smear : *P. falciparum*
Treatment : Fansidar (iii tab)
Quinine (IV x 3 days, po x 5 days)

Day 2 : Afebrile within 8 hours

Day 5 : Smear : Negative
Treatment : Bactrim (po x 5 days)

Case 785/21 Male nurse :

The patient was hospitalized and treated for *P. falciparum* malaria and then was placed on Fansidar prophylaxis (iii tablets at the beginning of the month) for two months.

Day 1 : (four days after 2nd prophylactic dose) :
febrile and vomiting

Smear : Negative

Day 2 : Smear : *P. falciparum*