RECRUDESCENCE, POOR RESPONSE OR RESISTANCE TO QUININE OF FALCIPARUM MALARIA IN THAILAND

NIBHA JAROONVESAMA, TRANAKCHIT HARINASUTA* and LAVAN MUANGMANEE

Department of Medicine, Faculty of Medicine and Siriraj Hospital, Mahidol University and *Hospital for Tropical Diseases, Bangkok, Thailand.

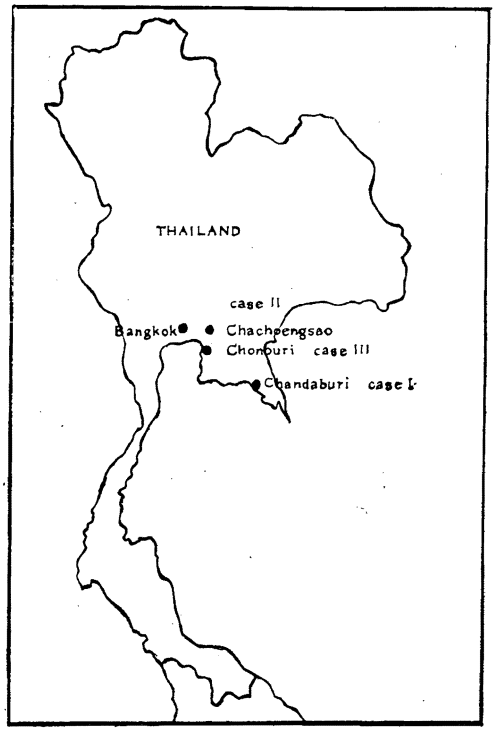
INTRODUCTION

Falciparum malaria has until recently been sensitive to treatment with quinine, although variations in the response of different strains have been observed for many years. Since 1960, the recognition of cases resistant to chloroquine phosphate, amodiaquine hydrochloride, and other standard antimalarials has caused concern over the possible development of resistance to quinine. It has been observed that cases of malaria, caused by a strain of *Plasmodium falciparum* isolated in 1969 in the United states from the soldiers returning from Vietnam, did not merely recrudesce following lengthy courses of quinine but in some instances failed to show the usual initial response to the treatment despite demonstrable normal absorption of quinine (Clyde *et al.*, 1970). The movement of people to and from endemic areas in Vietnam, Cambodia, and Thailand suggests that physicians will increasingly be confronted by this problem in the future.

We report 3 patients with falciparum malaria, admitted to the Siriraj Hospital, Bangkok, who failed to response to treatment with quinine. Two cases had recrudescence after 3 and 4 weeks of convalescene and another case failed to response to quinine 10 gr thrice daily for 14 days (total 22.7 gm base).

Case I

A Thai male aged 24 came to the hospital with a history of high fever for 4 days and unconsciousness for one day. The patient



Map of Thailand showing places where recrudescences and poor response or resistant *P. falciparum* malaria were observed after treatment with quinine.

recalled that 11 days prior to admission he visited Chantaburi an area endemic for malaria some 330 km from Bangkok and stayed there for 3 days. Four days after his return he developed a very high fever with chills associated with dysenteric symptoms. He was then treated by a private doctor and the dysenteric symptoms disappeared but the high fever remained. He went to see another doctor and tonsillitis was diagnosed and treated. The fever worsened and uncon-

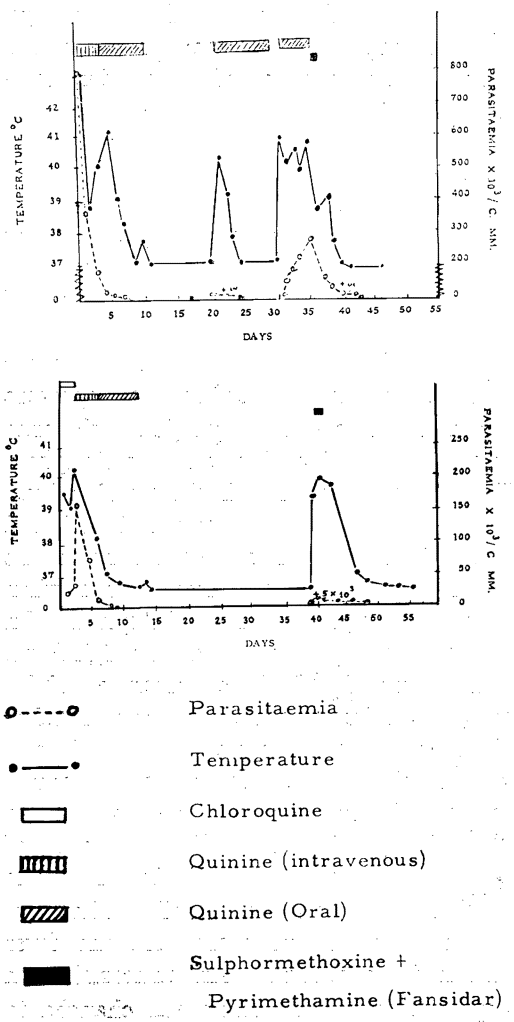
sciousness developed so he was brought to the hospital. Physical examination on admission revealed a semicomatose patient. His oral temperature was 41.8°C, pulse 120/min and blood pressure 110/70 mm Hg. There was moderate jaundice and a palpable liver about 2 finger breadths below the right costal margin. The spleen was not palpable. The pupils were equal on both sides and reacted to light. All reflexes were normal. No other neurological signs were detected. Numerous asexual forms of *Plasmodium falciparum* were found by routine laboratory examination of the blood. Bile was detected in the urine.

Treatment with quinine dihydrochloride 0.6 gm in 50 cc 50% glucose was given as a slow intravenous injection every 8 hours and cortisone in the form of Oradexon(R) 10 mg intravenously every 6 hours. Because of changes in the coagulogram, heparin 5,000 units intramuscularly every 6 hours was administered. Supportive and symptomatic therapy was given. He regained consciousness on the following day. A malaria parasite count was performed daily and parasitaemia gradually decreased until it became negative on the 7th day (Fig. 1). The quinine dihydrochloride was changed to quinine sulphate orally on the third day of treatment at a dosage of 1.8 gm daily for 7 days. The cortisone therapy was tailed off within 3 days. The heparin was stopped on the third day. The patient improved markedly. He was then discharged from the hospital. A blood smear was performed every week during the convalescent period. The result was negative until the first day of the third week, (21 days after the first attack) when one ring form of *P. falciparum* was found in the thick blood film. On the following day a very high fever developed with chills, although no other symptoms were detected. Quinine sulphate 1.8 gm daily was given orally for 10 days. Parasitaemia could not be detected until the second recrudescence on the 31st day of the disease when asexual forms of *P. falciparum* were again detected. Quinine sulphate was given again at the same dosage for 5 days. The drug was discontinued since the number of parasites had increased and the patient had a persistently high fever. So sulphormethoxine 1,000 mg and pyrimethamine 50 mg (Fansidar(R) 2 tablets) were administered as a single dose. The parasitaemia and fever then disappeared within 5 days. In follow-up blood smears no malarial parasites were detected after Fansidar treatment (Fig. 1).

Case II

A Thai male 29 years old gave a history of going to a forested area in Chachoengsao district 100 km east of Bangkok for 17 days previously and staying there for 3 days. He had taken prophylactic chloroquine for malaria on the day before his departure and during his stay in the jungle but the drug was discontinued on his return to Bangkok. He experienced fever with chills and polyarthralgia 2 days before admission and had acute diarrhoea with severe vomiting on the second day. He was semiconscious when he was brought to Siriraj Hospital. On admission the patient had a very high fever, temperature 39.5°C., blood pressure 110/80, and his pulse was 120/min and regular. His liver and spleen were not palpable and no other abnormalities were detected. Asexual forms of *Plasmodium falciparum* were found in the thin and thick blood films. A course of chloroquine phosphate, (total dose 1,500 mg base), for 3 days was given orally. The parasitaemia (Fig. 2) increased and the fever remained very high. An urticarial rash appeared so the treatment was changed to quinine dihydrochloride 0.6 gm in 50 cc 50% glucose given intravenously very slowly every 8 hours, and 10 mg of Oradexon(R) intravenous every 6 hours. Quinine dihydro-

chloride was replaced by oral quinine sulphate 1.8 gm per day on the 3rd day of quinine therapy, and it was discontinued on the 10th day. Oradexon was tailed off as the patient regained consciousness. All the symptoms and fever disappeared within 3 days and the malarial parasite was not found in the peripheral blood after the 7th day of treatment (Fig. 2). He was discharged after 3 daily



Figs. 1, 2—Show recrudescences of *P. falciparum* malaria after treatment with curative dose of quinine and completely cured by sulphormethoxine 1000 mg and pyrimethamine 50 mg. (Fansidar 2 tablets) single dose.

blood films were negative for parasites. At home he was well for 20 days, when moderate fever developed. But thin and thick blood films were negative for malaria. He was treated by a private doctor and the fever disappeared for 6 days but then developed again, so he returned to the hospital. A blood smear was performed and ring forms of *P. falciparum* were detected. Fansidar(R) 2 tablets was given as a single dose. Blood films were negative for malaria parasite 10 days after Fansidar(R) therapy.

Case III

A Thai male aged 41 was admitted into the medical ward of Siriraj Hospital with the chief complaint of fever for 6 days after working in a rural area of Chonburi district 100 km east of Bangkok for 6 days. On admission, the temperature was 39°C, blood pressure 120/70, pulse 100/min regular. He was anaemic, slight jaundiced and dehydrated. The liver was palpable 2 finger breadths but the spleen was not palpable. Blurred consciousness was the only neurological sign detected. The thin blood film revealed ring forms of *P. falciparum*. The parasite counts are shown in Fig. 3. A

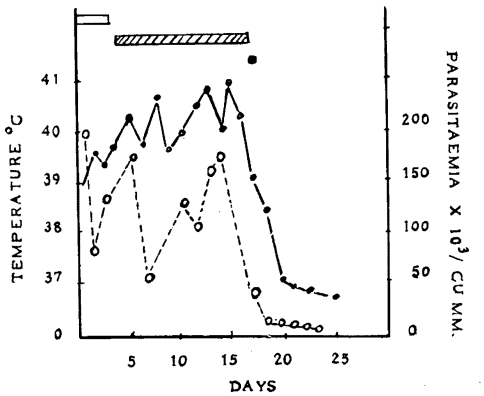


Fig. 3—Shows poor response or resistant to quinine (30gr/d for 14 days) of *P. falciparum* malaria and completely cured by sulphormethoxine 1000 mg and pyrimethamine 50 mg. (Fansidar 2 tablets) single dose.

course of chloroquine sulphate orally (1,500 mg total dose) for 3 days was given but no improvement was observed. The parasitaemia was persistently high and the patient's general condition was poor due to high fever and anaemia (haematocrit 15 per cent). So the treatment was changed to quinine sulphate orally 1.8 gm daily for 14 days. The parasitaemia decreased only 3 days after treatment was begun and then it rose again and remained high. A qualitative test for quinine in the blood was positive. The patient's condition deteriorated so Fansidar(R) (sulphormethoxine 1,000 mg + pyrimethamine 50 mg) was administered intramuscularly in a single dose. The temperature then returned to normal in 3 days and the blood smear became negative in 8 days (Fig. 3). The patient's general condition improved quickly and satisfactorily. A blood examination for the malaria parasite performed every week for 7 weeks was negative. The patient remained asymptomatic and to date has had no relapse of malaria.

DISCUSSION

This report suggests that there were recrudescences, poor response or resistance of *P. falciparum* malaria in Thailand after treatment with quinine. Pinswasdi and Charoenkan (1965) reported a case of *P. falciparum* infection from Rayong province which was insensitive to chloroquine and showed poor response to intensive oral quinine therapy.

There is as yet no internationally accepted definition of quinine resistance. According to the classification of resistance to chloroquine by WHO (1967, 1973), there are three levels of resistance and the recommended symbols are R I, R II, R III. If this classification could be used for these three patients then the first case resembled R I and later R III, the second case was R I and the third case was R III. The first two patients had been given quinine intravenously 1.8 gm per day only for 3 days and continued with oral quinine at the same dosage for 7 days. Hall (1972) reported on US troops with falciparum malaria which recrudesced following treatment with quinine sulphate, pyrimethamine and dapsone or sulphonamide orally. His studies indicated that infused quinine was more effective than oral quinine in achieving a radical cure of the recrudescent infections. The possible cause seemed be an inadequate plasma level of the orally administered drug which may have been a factor which could have accounted for some of the recrudescences. There are several possible causes for reduced plasma levels. Oral quinine causes nausea and vomiting and also acute malaria produces vomiting especially following ingestion of quinine (Sheehy and Reba, 1967). It has been reported that enteric coated quinine tablets may become hard and insoluble in the gastrointestinal fluids resulting in reduced dissolution and thus poor absorption of the drug (Rollo, 1970). But these three patients had no nausea, vomiting, diarrhoea or abdominal distension and enteric coated quinine tablets were not used during oral quinine therapy. Other possible cause of decreased absorption in the patients could have been non specific jejunitis, (Sheehy *et al.*, 1968), intestinal worms (Fine and Goldschlager, 1970), or an intestinal lesion which may occur in acute falciparum malaria, (Olsson and Johnston, 1969; Karney and Tong, 1972). These possible causes of reduced absorption cannot be excluded from our three patients. However, good results were obtained when the treatment was changed to sulphormethoxine and pyrimethamine (Fansida(R)). Reinfection was excluded because the three patients did not go back to the areas endemic for malaria. Concerning the effectiveness of the non-enteric coated quinine tablets, they were proven to be highly effective

as the same lot was used for other malaria patients. The cause of recrudescence or resistant *P. falciparum* in our three patients could have been inadequate quinine plasma levels due to oral drug administration. Hall *et al.*, (1972) showed in a randomized cross-over study in healthy volunteers that quinine infusion produced significantly higher plasma levels than oral quinine.

Evidence of recrudescences and poor response to quinine has been increasing (Legters *et al.*, 1965; Bartelloni *et al.*, 1967; Sheehy and Reba, 1967; Reback, 1968; Reed *et al.*, 1968). Recently Hall (1973) reported a 12% recrudescence rate among US Army soldiers with falciparum malaria in Vietnam during the years 1969 to 1970 who were treated with a combination of quinine, pyrimethamine and dapsone or sulphonamide. In South America and Southeast Asia a number of strains of chloroquine resistant *P. falciparum* have been found to exhibit cross resistance to quinine (Peters, 1970). So new and more effective drugs are needed for treatment of drug resistant malaria.

SUMMARY

A report of three cases of recrudescences, poor response or *P. falciparum* malaria resistant to quinine therapy at the Siriraj Hospital are presented.

The first case was treated with quinine dihydrochloride 0.6 gm every 8 hours intravenously for 3 days and followed by oral quinine sulphate at the same dosage for 7 days. The first and second recrudescences occurred 21 and 31 days after the first attack and were treated with 10 and 5 day courses of oral quinine respectively. The second and the third cases were first treated with chloroquine 1,500 mg but the parasites showed resistance to this drug. The treatment for the second case was changed to intravenous and oral quinine at the same dose and for the same duration as the first case. A recrudescence was observed 26 days after the first attack. For the third case, oral quinine 0.6 gm thrice daily was administered for 14 days but the parasites showed insensitivity or resistance to quinine. Eventually all three patients were completely cured after administration of sulphormethoxine 1,000 mg and pyrimethamine 50 mg single dose (Fansidar(R) 2 tablets).

REFERENCES

BARTELLONI, P.J., SHEEHY, T.W. and TIGERTT, W.D., (1967). Combined therapy for chloroquine resistant *Plasmodium falciparum* infection. *J.A.M.A.*, *199*: 173.

CLYDE, D.F., MILLER, R.M., DUPONT, H.L. and HORMICK, R.B., (1970). Treatment of falciparum malaria caused by strian resistant ot quinine. *J.A.M.A.*, *213*: 2041.

FINE, A.H. and GOLDSCHLAGER, A.W., (1970). Subclinical intestinal parasitic infections in military personal with malaria. *Ann. Intern. Med.*, *73* : 857.

HALL, A.P., (1972). Quinine infection for recrudescences of falciparum malaria in Vietnam a controlled study. *Amer. J. Trop. Med. Hyg.*, *21* : 851.

HALL, A.P., CZERWINSKI, A.W., MADONIA, E.C. and EVENSEN, K.L., (1972). Plasma quinine levels following tablets, capsules or intravenous infusion. *Clin. Pharmacol. Ther.*, *13* : 140.

HALL, A.P., (1973). Recrudescent falciparum malaria in Vietnam. *Amer. J. Trop. Med. Hyg.*, *22* : 296.

KARNEY, W.W. and TONG, M.J., (1972). Malabsorption in *Plasmodium falciparum* malaria. *Amer. J. Trop. Med. Hyg.*, *22* : 1.

LEGTERS, L.J., WALLACE, D.K., POWELL, R.D. and POLLACK, S., (1965). Apparent to chloroquine, pyrimethamine, and

quinine strain of *Plasmodium falciparum* from Vietnam. *Milit. Med., 130* : 168.

OLSSON, R.A. and JOHNSTON, E.H., (1969). Histopathologic changes and small-bowel absorption in falciparum malaria. *Amer. J. Trop. Med. Hyg., 18* : 355.

PETERS, W., (1970). Chemotherapy and drug resistance in malaria. Academic press. London and New York.

PINSWASDI, K. and CHAREONKWAN, P., (1965). Sluggish response of a case of falciparum malaria to intensive quinine therapy. *J. Med. Ass. Thailand, 48* : 386.

REBACK, H., (1968). Medical problems from Vietnam. *Ann. Intern. Med., 69* : 168.

REED, W.P., FEINSTEIN, M. and STEIGER, B.W., (1968). Early experience in the treatment of falciparum malaria from Southeast Asia. *J.A.M.A., 205* : 131.

ROLLO, I.M., (1970). Drugs used in the chemotherapy of malaria, pp. 1095-1124. *In* L.S. Goodman and A. Gilman (Eds). *The Pharmacological Basis of Therapeutics*. 4th ed. MacMillan Co., New York.

SHEEHY, T.W. and REBA, R.C., (1967). Treatment of chloroquine resistance *Plasmodium falciparum* infections in Vietnam. *Ann. Intern. Med., 66* : 616.

SHEEHY, T.W. and REBA, R.C., (1967). Complications of falciparum malaria and their treatment. *Ann. Intern. Med., 66* : 807.

SHEEHY, T.W., LEGTERS, L.J. and WALLACE, D.K., (1968). Tropical jejunitis in Americans serving in Vietnam. *Amer. J. Clin. Nutr., 21* : 1013.

WHO, (1967). Chemotherapy of malaria. *WHO, Techn. Rep. Ser., 375* : 42.

WHO, (1973). Chemotherapy of malaria and resistance to antimalarials. *WHO, Techn. Rep. Ser., 529* : 30.