Polyresistant Malaria in Gurkha Soldiers Returning from Papua New Guinea: Treatment and Prevention

Major A Henderson,*
MRCP, RAMC

Major J Simon,
MRCP, RAMC

Major W Melia,
MRCP, RAMC

Major J Navein,
MB, RAMC

Capt J McCallum,
MB, RAMC

Medical Division BMH Hong Kong

SUMMARY: Two company strength exercises to Papua New Guinea produced 21 malaria casualties of whom 16 had potentially fatal falciparum infections. The chemotherapy and prevention of polyresistant malaria from Papua New Guinea and the threat posed to the Hong Kong environment regarding malaria re-introduction are discussed.

Introduction

The British Army holds periodic field exercises in Papua New Guinea. The lowland coastal and jungle areas where training takes place are malarious with intense transmission of *Plasmodium vivax* and *Plasmodium falciparum*¹.

The intensity of the malaria transmission and the complex drug resistance profile of the plasmodia poses a serious threat to military operations. The falciparum species is resistant to chloroquine and probably to pyrimethamine-sulfadoxine (Fansidar) while the vivax species (Chesson strain) is tolerant to conventional doses of primaquine¹⁻⁴. The situation regarding proguanil (Paludrine) and pyrimethamine is unclear but as resistance to both drugs is widespread, particularly in areas of chloroquine resistant falciparum malaria, neither should be relied upon in Papua New Guinea¹⁻⁷.

Between December 1984 and November 1985 two company strength exercises (246 men) produced 21 cases of malaria including two cases of cerebral malaria. This paper examines the threat of malaria to British military operations in Papua New Guinea and discusses the danger of malaria reintroduction posed by infected soldiers returning to malaria receptive areas in the New Territories of Hong Kong.

Patients and Methods

Exercise I (see Table I)

The exercise which took place at the end of 1984, involved 126 Gurkha soldiers. Malaria chemoprophylaxis was with proguanil 200 mg daily. Compliance however was probably poor (Table 1). Physical

*Consultant Physician, British Military Hospital, Hong Kong.

antimosquito measures (long sleeves and trousers at night, insect repellents, mosquito nets) were used extensively because of the biting nuisance. On return to Hong Kong 17 men were admitted to the British Military Hospital (BMH) Hong Kong. Fifteen presented within a few days of return with fever, headache, shivering, generalised aches and pains. Two rapidly became drowsy and confused due to cerebral malaria. One presented atypically with fever and profuse diarrhoea. Following the diagnosis of 15 cases the rest of the company were screened for malaria infection by thick film examination. One asymptomatic case of vivax malaria was found while another (also with a vivax infection) was missed and presented later with clinical malaria.

The parasitological diagnosis was falciparum only in six, vivax only in five and mixed falciparum and vivax in six. One man (Case 7) with vivax malaria relapsed after treatment and was readmitted.

On admission all patients were assessed by an experienced member of the medical division. Blood was taken for malaria species differentiation, parasite density, haemoglobin, white cell count, platelet count, urea and electrolytes, liver function tests, prothrombin time and glucose-6-phosphate dehydrogenase (G6PD) levels. A chest X-ray was also performed. Patients with complications or high falciparum densities were admitted to the intensive care unit (ICU). Patients with falciparum malaria all received quinine, initially supplemented by Fansidar, but later, because of worries about Fansidar resistance, by oxytetracycline. A single gametocidal dose of primaquine 45 mg completed the

Table I
Patients with Malaria from Exercise I

Patient	Admission Date	Plasmodial Species	G6PD	Prophylaxis	Compliance with Prophylaxis	Comments
1	18/12/84	F + V	N	Paludrine 200 mg Daily	Good	
2	18/12/84	F	N	Paludrine 200 mg Daily	Good	Cerebral Malaria
3	18/12/84	F + V	N	Paludrine 200 mg Daily	Poor	Also took Maloprim
4	19/12/84	F	N	Paludrine 200 mg Daily	Poor	Also took Maloprim
5	19/12/84	F	N	Paludrine 200 mg Daily	Poor	
6	19/12/84	F + V	N	Paludrine 200 mg Daily	Poor	Also took Maloprim
7	19/12/84	V	N	Paludrine 200 mg Daily	Poor	Also took Maloprim. Relapsed.
8	20/12/84	F + V	N	Paludrine 200 mg Daily	Good	
9	20/12/84	F	N	Paludrine 100 mg Daily	Good	Cerebral Malaria
10	21/12/84	F	N	Paludrine 100 mg Daily	Good	
11	21/12/84	V	N	Paludrine 100 mg Daily	Good	
12	12/12/84	F	N	Paludrine 100 mg Daily	Good	
13	24/12/84	F + V	N	Paludrine 100 mg Daily	Poor	
14	28/12/84	F + V	N	Paludrine 200 mg Daily	Good	
15	11/1/85	V	N	Paludrine 100 mg Daily	Poor	
16	18/1/85	V	N	Paludrine 100 mg Daily	Good	
17	20/3/85	V	N	Paludrine 200 mg Daily	Good	

F = Falciparum V = Vivax N = Normal G6PD = Glucose 6-Phosphate Dehydrogenase.

chemotherapy. Vivax malaria was treated by chloroquine followed by primaquine 7.5 mg twice daily for 14 days. The dose of primaquine was later increased to 7.5 mg thrice daily for 14 days because of drug tolerance by the Chesson strain. All patients recovered completely and had cleared parasites within five days. The current treatment regimen is outlined in Table II.

Exercise II (see Table III)

This exercise involving 120 Gurkha soldiers took place towards the end of 1985. Malaria chemoprophylaxis was with proguanil 200 mg daily plus chloroquine base 300 mg weekly. Compliance was rigorously enforced as were physical antimosquito measures. Four men developed clinical malaria while in Papua New Guinea. Thin films revealed heavy falciparum infections and all were treated locally. Three received quinine, but one (Patient 18) was given chloroquine. He suffered a clinical and parasitological relapse within a few days of returning to Hong Kong and was admitted to hospital. Treatment was along the lines laid out in Table II.

The other three on return had no evidence of malaria on thick film examination but as they had not received gametocidal therapy in Papua New Guinea all were

given a single dose of primaquine 45 mg.

Discussion

Malaria in Papua New Guinea presents special problems for the Army and the return to Hong Kong of soldiers harbouring plasmodial gametocytes entails a grave risk to the ecology of Hong Kong. The various facets of the treatment and prevention of malaria and the protection of the environment will be discussed separately.

1. Management of Clinical Malaria.

(A) **Falciparum.** Untreated falciparum malaria carries a high mortality in non-immune subjects. Patients with high parasite counts (more than 10^5 infected red cells per mm^3) anaemia, (haemocrit below 30%) or complications (especially impaired consciousness) are at grave risk⁸. Twelve patients from Exercise I and one from Exercise II developed clinical falciparum malaria in Hong Kong (three others from Exercise II had falciparum malaria successfully treated in Papua New Guinea). Because of chloroquine resistance, all the clinical cases were given quinine which is a highly effective rapidly acting schizonticide⁹. The two patients with early cerebral malaria (cases 1 and 9) were given

quinine 10 mg/kg body weight infused over 4 hours and repeated at 8 hours. This is safe and effective for most areas except in Thailand and possibly parts of South America where a 'loading dose' of 20 mg/kg is necessary^{4,9-11}.

In the remainder, quinine was given by mouth. It is essential in patients with reduced consciousness to monitor blood sugar frequently as dangerous hypoglycaemia may occur. The pathogenesis of hypoglycaemia is complex. It may occur as a terminal event in untreated falciparum malaria but the prevalence of hypoglycaemia is higher in patients treated with quinine which is thought to cause hyperinsulinaemia¹². Steroids and heparin were not used as several recent studies have failed to show benefit and one carefully controlled trial in Thailand showed dexamethasone was detrimental in cerebral malaria^{10,11,13,14,15}. The patients with cerebral malaria were given oxygen and fluid and electrolyte balance was meticulous because of the ever present dangers of pulmonary oedema and inappropriate ADH secretion^{8,9}.

Schizonticidal therapy was completed initially with a single dose of Fansidar (three tablets) but because of possible Fansidar resistance¹ this was subsequently replaced by oxytetracycline which has been shown to be superior to quinine alone in the radical cure of falciparum malaria^{9,11}. All patients recovered fully and all had cleared malarial parasites within five days. Treatment was completed by a single gametocidal dose of primaquine 45 mg⁴.

(B) **Vivax**. Chloroquine was used as a schizonticide and achieved rapid parasite clearance. Once the G6PD was known to be normal, primaquine 7.5 mg twice daily for 14 days was given to effect radical cure. This was later increased to 7.5 mg thrice daily because of primaquine tolerance by the Chesson strain of *Plasmodium vivax* which is prevalent in Papua New Guinea⁴. All patients

Table II
Treatment of Malaria from Papua New Guinea

Falciparum

Quinine Sulphate Orally 600 mg tds for 5 days*
Oxytetracycline 250 mg qid for 10 days+
Primaquine 45 mg as a single dose

Vivax

Chloroquine Base 600 mg orally at once
Chloroquine Base 300 mg 6 hours later
Chloroquine Base 150 mg 12 hourly for 4 doses
Primaquine 7.5 mg tds for 14 days‡

Mixed Vivax and Falciparum

Quinine Sulphate Orally 600 mg tds for 5 days
Oxytetracycline 250 mg qid for 10 days+
Primaquine 7.5 mg tds for 14 days‡

* Seriously ill patients should receive quinine 10 mg/kg infused over 4 hours.

+ If contraindicated, use clindamycin.

‡ Patients with normal G6PD only. If G6PD is subnormal, primaquine 45 mg once weekly for 8 weeks.

on the high dose primaquine regimen were screened for haemolysis with negative results. Patient 7 relapsed on low dose primaquine but was radically cured using the higher dose regimen. The only complication of the high dose was a severe generalised chloroquine induced pruritis in one patient. The mechanism of chloroquine pruritis is unclear but it is common, occurring in up to 20% of subjects exposed to the drug¹⁶.

Table III
Patients with Malaria following Exercise II

Patient	Admission Date	Plasmodial Species	G6PD	Prophylaxis	Treatment in Papua New Guinea
18	30/10/85	F	N	Paludrine 200 mg Daily Chloroquine 300 mg Weekly	Chloroquine. Relapsed in Hong Kong.
19	31/10/85	F	N	Paludrine 200 mg Daily Chloroquine 300 mg Weekly	Quinine
20	31/10/85	F	N	Paludrine 200 mg Daily Chloroquine 300 mg Weekly	Quinine
21	31/10/85	F	N	Paludrine 200 mg Daily Chloroquine 300 mg Weekly	Quinine

F = Falciparum N = Normal
G6PD = Glucose 6-Phosphate Dehydrogenase

(C) **Mixed Infection.** Patients with mixed infections were treated as for falciparum malaria except that the dose of primaquine was increased from a single 45 mg dose to 7.5 mg thrice daily for 14 days. Rapid cure was effected in all cases.

The current treatment regimen is outlined in Table II.

2. Prevention of Malaria in Papua New Guinea

Physical antimosquito measures are essential especially in areas where drug resistant plasmodia occur. During both the recent exercises in Papua New Guinea soldiers were strongly self-motivated regarding antimosquito measures because of the severe biting nuisance.

Chemoprophylaxis is more difficult. Because of wide geographical variations in parasite drug susceptibility and rapidly changing resistance profiles it is becoming increasingly difficult to formulate a uniform global policy for chemoprophylaxis⁹. Proguanil and pyrimethamine resistance is now widespread especially in areas where chloroquine resistant falciparum occurs, so both may be unreliable as monocomponent chemoprophylaxis in Papua New Guinea, although proguanil is simple to use and remarkably safe¹⁷. Chloroquine remains highly effective against vivax (and malariae) but is unreliable against Papua New Guinea falciparum strains. Falciparum resistance to Fansidar has been described¹. Both Fansidar and Maloprim are intrinsically weak against vivax infections and both are associated with serious, sometimes fatal side-effects^{6,17}. Although accurate comparisons between the different regimens during the recent exercises is not possible because of differences in compliance, the combination of proguanil 200 mg daily plus chloroquine base 300 mg weekly seems superior to proguanil alone, not only in reducing the overall casualty rate but in eliminating vivax infections. Unfortunately even dual chemoprophylaxis failed to abolish potentially fatal falciparum infections. Amodiaquine may be effective against chloroquine resistant falciparum as has been recently shown in Thailand¹⁸. This drug used alone or with proguanil may have a place in Papua New Guinea. An even more potent combination may be the new mefloquine – pyrimethamine – sulfadoxine combination which has been shown to be effective against polyresistant plasmodia¹⁹.

As can be seen from Table I compliance with chemoprophylaxis in the malaria victims was very poor during Exercise I. Of the 17 patients only five were taking proguanil 200 mg daily. The remainder were either using the wrong dose or were taking the drug irregularly or both. Four men were using proguanil – maloprim combinations irregularly. During Exercise II compliance was rigorously enforced. Although the combination of complex chemoprophylaxis and much improved compliance abolished vivax infections, cases of falciparum malaria still occurred although with reduced frequency.

3. Protection of the Environment

Until relatively recently malaria was endemic in Hong Kong with up to 2000 cases annually²⁰. The introduction of antimalarial measures in the 1950s gradually reduced indigenous transmission to zero by 1968²⁰. The mosquito ecology in the New Territories however remained favourable to malaria re-introduction and small numbers of indigenous cases have been reported annually since 1976¹⁸. Gurkha soldiers returning from Papua New Guinea harbouring gametocytes represent a serious threat to the malaria control programme in Hong Kong. The battalions are based and operate in the New Territories where malaria receptive vectors (*An. jeyporiensis* and *An. minimus* especially) abound. The introduction of malaria in this context is especially unwelcome because of the complex drug resistance of the plasmodia. Minimising the environmental risk falls into several areas:

(A) **Prevention of malaria transmission to soldiers in Papua New Guinea.** This has already been discussed.

(B) **Rapid case detection.** The longer the infected soldier is exposed to receptive vectors the greater the risk. During Exercise I the mean duration of symptoms before the institution of effective therapy was six days (range 2-21). This was mostly due to delay in self-referral although in four cases (all falciparum) the early symptoms were thought to be due to "flu" resulting in a delay of several days before the gravity of the situation was realised. Falciparum malaria in its early stages may be entirely non-specific in its presentation and can closely resemble a mild viral illness. The subsequent delay in diagnosis exposes the patient to great danger as sudden clinical progression to death can occur even in patients who at first sight do not appear to be seriously ill¹². The problem was solved by alerting battalion medical officers, followed by a search for febrile patients and rapid thick film screening. Subsequently all men with fever, shivering or headache were ordered to report immediately to their medical officer.

(C) **Prevention of Relapse.** The resistance profile of Papua New Guinea malaria predisposes to relapse. As parasitological relapse may precede clinical relapse a danger to the environment exists. Following the relapse of Patient 7 all men with vivax malaria received increased doses of primaquine. Patient 18 who was given chloroquine for falciparum malaria in Papua New Guinea not surprisingly relapsed. Our current treatment policy (Table II) appears to effect rapid cure and prevent relapse.

(D) **Detection of Relapse.** To detect subclinical parasitological relapse all patients were screened by thick film examination monthly for six months after the completion of treatment.

(E) **Population Screening.** Following the high prevalence of malaria after Exercise I the entire company was screened for subclinical malaria by blood film examination. It is essential to use thick films for this

purpose and to screen approximately 100 high power fields before pronouncing a negative result^{21,22}. If malarial parasites are found species differentiation can then be achieved by thin film examination. One asymptomatic patient with vivax malaria was found while another also with vivax malaria was missed and presented with clinical malaria later. Because of the low pick-up rate and considerable logistical burden screening was not repeated after Exercise II. It may have to be reconsidered however should late cases of malaria occur.

(F) Gametocidal Therapy. Although both quinine and chloroquine rapidly destroy schizonts and effect clinical cure neither destroys gametocytes. The gametocyte may remain infective to mosquitoes for several weeks. Primaquine is the only effective gametocidal drug currently available. In patients with vivax malaria specific gametocidal therapy is not a practical problem because primaquine is routinely used to effect radical cure. However permanent clinical cure of falciparum malaria can be achieved by schizonticidal drugs alone so separate gametocidal therapy must be considered. In areas where falciparum malaria is endemic gametocidal therapy does not appear to significantly reduce transmission in the community⁹. However in Hong Kong where endemic transmission is trivial but where receptive vectors abound adjuvant gametocidal therapy to prevent malaria becoming re-established is essential. Primaquine 45 mg as a single dose appears to be highly effective in this regard⁴. In our patients with falciparum malaria including the soldiers treated in Papua New Guinea a single dose of primaquine 45 mg was given as soon as the G6PD was known to be normal.

The malaria threat to the Army posed by Papua New Guinea is likely to continue. Urgent research into the local malaria situation is required to determine the best chemoprophylaxis. This must be supplemented by education of the Gurkha battalions to increase their motivation regarding prophylaxis and drug compliance. The importance of antimosquito measures can not be over-emphasised. Doctors treating men who have recently been in Papua New Guinea need to be familiar with the special drug resistance problems and need to be aware of the atypical presentations of falciparum malaria.

REFERENCES

- 1 PUBLIC HEALTH LABORATORY SERVICE MALARIA REFERENCE LABORATORY. Malaria prophylaxis. *Br Med J* 1983; **286**: 787-789.
- 2 WALKER E and WILLIAMS G. ABC of Healthy Travel: Malaria prophylaxis. *Br. Med J* 1983; **286**: 781-783.
- 3 BRUCE-CHWATT LJ. Mosquitoes, Malaria and War; Then and Now. *J R Army Med Corps* 1985; **131**: 85-99.
- 4 PETERS W. Antimalarial drug resistance; an increasing problem. *Br Med Bull* 1982; **38**: 187-192.
- 5 WHO WEEKLY EPIDEMIOLOGICAL RECORD 1982; **52**: 381-384.

- 6 PUBLIC HEALTH LABORATORY SERVICE MALARIA REFERENCE LABORATORY. Malaria prophylaxis for long term visitors. *Br Med J* 1983; **287**: 1454-1455.
- 7 ROSS INSTITUTE. Malaria prevention in travellers from the United Kingdom. *Br Med J* 1983; **283**: 214-218.
- 8 WEATHERALL DJ, LEDINGHAM JG G and WARRELL DA (Ed). Oxford Textbook of Medicine. Oxford University Press. Oxford 1983. P.5: 393-5: 399.
- 9 WHITE NJ and WARRELL DA. Clinical management of chloroquine resistant falciparum malaria in South-East Asia. *Trop Doct* 1983; **13**: 153-158.
- 10 HALL AP. Treatment of Malaria. *Br Med J* 1976; **3**: 323-328.
- 11 GILLES EM. Malaria. *Medicine International* 1984; **5**: 141-145.
- 12 WHITE NJ et al. Severe hypoglycaemia and hypoinsulinaemia in falciparum malaria. *New Eng J Med* 1993; **309**: 61-66.
- 13 LOOAREESUWAN S, et al. Do patients with cerebral malaria have cerebral oedema. A computed tomography study. *Lancet* 1983; **1**: 434-437.
- 14 CHAROENLARP P, VANJANONTA S and CHANPANYAPORN P. The effect of prednisolone on red cell survival in patients with falciparum malaria. *Southeast Asian J Trop Med Public Health* 1979; **10**: 127-131.
- 15 WARRELL DA, et al. Dexamethasone proves deleterious in cerebral malaria. Double blind trial of 100 comatose patients. *New Eng J. Med* 1982; **306**: 313-319.
- 16 OLATUNDE A and OBIH PO. Use and misuse of 4-aminoquinoline antimalarials in tropical Africa. *Trop Doct* 1981; **11**: 97-101.
- 17 CENTRES FOR DISEASE CONTROL. Adverse reactions to Fansidar and updated recommendations for its use in the prevention of malaria. *Morbidity and Mortality Weekly Report* 1985; **33**: 713-714.
- 18 LOOAREESUWAN S et al. Intravenous amodiaquine and oral amodiaquine erythromycin in the Treatment of chloroquine-resistant Falciparum Malaria. *Lancet* 1993; **II**: 805-808.
- 19 WIN K et al. Comparison of Mefloquine with sulfadoxine-pyrimethamine compared with two sulfadoxine-pyrimethamine combinations in malaria prophylaxis. *Lancet* 1985; **II**: 694-695.
- 20 PAIK YH and THEVASAGAYAN ES. Report of a Field Visit to Hong Kong December 7-14 1983. *WHO* 1983.
- 21 CHEESEBROUGH M. The blood film as a routine screening test in rural tropical hospitals. *Trop Doct* 1981; **11**: 189-189.
- 22 WORLD HEALTH ORGANISATION. Terminology of Malaria and of Malaria Eradication. *WHO* 1933 Geneva.

Editor's Footnote

Tri-Service policy on malaria chemoprophylaxis is currently under review and is expected to be promulgated in the near future.