Malaria Chemoprophylaxis with a Proguanil – Chloroquine – Maloprim Combination in Papua New Guinea

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SUMMARY: Proguanil 200mg daily and chloroquine base 300mg weekly along with maloprim 1 tablet weekly was used as malaria chemoprophylaxis for 140 Hong Kong based soldiers on a seven-week jungle exercise in a holoendemic malarial area of Papua New Guinea. On return from exercise all personnel were treated with primaquine 7.5mg three times daily for a two week period. One soldier developed P. falciparum on the exercise whilst taking chemoprophylaxis and four subsequently developed P. vivax malaria after cessation of chemoprophylaxis.

Introduction
Detailed epidemiological information about malaria in Papua New Guinea (PNG), the implications for the British Army, and recommendations for malaria chemoprophylaxis in PNG have recently been published in this Journal. A company level Infantry Training Exercise was held in PNG in 1986. Malaria chemoprophylaxis based on recommendations by Henderson was implemented and this paper outlines the efforts made to ensure and monitor compliance and details the effectiveness of this chemoprophylactic regime.

Patients and Methods
One hundred and forty soldiers took part in a military exercise in PNG from 28 August 1986 until 7 October 1986. This exercise was held in the lowland jungles of East Sepik and in the hinterland of Port Moresby. All were screened for red cell glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to the exercise. Malaria chemoprophylaxis was implemented using proguanil 200mg daily, chloroquine 300mg weekly and maloprim one tablet weekly. This was commenced one week prior to travel to PNG and was to be continued for four weeks after return. All exercise personnel were shown a film concerning malaria prevention and instructed about personal anti-mosquito procedures and the requirement for compliance with the chemoprophylactic regime.

Soldiers were paraded on each day of the exercise and seen to take their drugs, a written record being kept of all drugs issued against individual names. This was continued on their return. During the exercise a reminder drawing attention to the serious hazard of malaria in PNG was published in exercise orders weekly on the day that chloroquine and maloprim were to be taken. All other precautions regarding clothing, mosquito nets, “knock down” spray, insect repellent, swing fogging and destruction or removal of potential mosquito breeding areas were employed.

The hypnozoites of the Chesson strain of P. vivax found in PNG are resistant to the action of blood schizonticides and conventional doses of primaquine. It was considered possible that clinical vivax malaria could occur in heavily exposed soldiers after they had stopped chemoprophylaxis. It was therefore decided to give all personnel a hypnozoiticidal dose of primaquine on return from PNG. For the Chesson strain this is 7.5mg three times daily for fourteen days. As a side benefit, any falciparum gametocytes would also be destroyed. The Hong Kong Government Medical and Health Department are obviously concerned that resistant strains of malaria are not introduced into the New Territories of Hong Kong and the above measures helped to allay their fears.

In addition to maintaining a register of drug issue following their return from exercise, compliance was tested by obtaining urine samples from forty-six of the exercise personnel chosen randomly and these were tested for the presence of proguanil by the method of Gage and Rose.

Results
There were no cases of G6PD deficiency found. No side effects of the chemoprophylactic regime were reported. During the exercise compliance registers were well maintained and compliance excellent.

Of the forty-six urine samples tested for the presence of proguanil five were negative and three only weakly positive. The remaining thirty-eight were unequivocally positive. The soldiers with negative or weak positive results were interviewed and denied non-compliance. This was verified by the compliance register. At the time of interview all eight were invited to produce a second urine sample before they had further access to proguanil and all eight were found positive for the presence of proguanil.

During the period of the exercise there was one case of malaria. This presented with symptoms of fever and rigors. A diagnosis of falciparum malaria was made on blood smear examination. This was treated successfully with quinine hydrochloride 600mg twice daily for three days on completion of which three tablets of fansidar were given. The patient had been fully compliant with his chemoprophylaxis.
After return from exercise there were four cases of vivax malaria diagnosed in personnel who had no other history of exposure other than PNG. The first presented on 8 November 1986 with a three day history of malaise and fever. Blood films were positive for *P. vivax* trophozoites. He had been fully compliant with his chemoprophylaxis up until three weeks after return from PNG. At this point he had stopped all chemoprophylaxis due to an administrative error. The second case of *P. vivax* was diagnosed in Kathmandu in December 1986. This patient had been on the PNG exercise and had recently arrived in Kathmandu on leave. He had taken a full course of chemoprophylaxis.

A third soldier presented on 16 January 1987 with a four day history of muscle aches and fever. A blood film was positive for *P. vivax* malaria. He likewise had stopped his chemoprophylaxis three weeks after return from PNG. A fourth case of vivax malaria presented on 2 March with a three day history of malaise, headache, joint pains and fever. He had taken a full course of chemoprophylaxis.

Enquiries made at the time of presentation of the first case of vivax malaria revealed that a total of 43 soldiers had stopped taking chemoprophylaxis three weeks after their return from exercise due to an administrative misunderstanding. At this stage it was felt inappropriate to resume chemoprophylaxis but these soldiers were told to report early any febrile illness in the following six months.

**Discussion**

Chloroquine resistant *P. falciparum* has been reported in all districts of PNG. Most of the resistance was at the RI level. Chloroquine, however, remains active against *P. vivax, P. malariae* and *P. ovale* in PNG.

A recent study in PNG reported maloprim to be fully effective against *P. falciparum*, whilst allowing low-grade *P. vivax* breakthrough. Maloprim one tablet weekly in combination with chloroquine base 300mg weekly has been recommended as an effective malarial chemoprophylaxis in PNG. This combination has virtually eliminated *P. falciparum* from Australian soldiers in PNG. In PNG where G6PD deficiency is not uncommon no cases of haemolytic anaemia, nor other serious side effects have been seen in the PNG Defence Force with 15,000 man years of maloprim use.

At the time this exercise took place proguanil 200mg a day was being used for malaria chemoprophylaxis by all soldiers serving in Hong Kong. It was felt appropriate to continue this in the regime used for chemoprophylaxis in PNG. On a previous exercise in the Sepik district of PNG only 13% of soldiers using proguanil alone developed malaria suggesting some degree of protection is afforded. An added advantage is the ease with which proguanil can be measured in urine samples as a means of screening for compliance.

On a previous exercise in PNG employing one hundred and twenty soldiers and using a proguanil-chloroquine combination as malaria chemoprophylaxis nineteen cases of malaria were recorded. All nineteen developed falciparum malaria, eleven of these having a mixed infection with vivax malaria. This study demonstrates that by using a proguanil-chloroquine-maloprim combination there was a significant reduction in the incidence of falciparum malaria (p < 0.001). There was also a reduction in the number of cases of vivax malaria (p = 0.1). Both studies involved a closely supervised group of non-immune subjects in the same area of PNG during the same period of the year.

The introduction of a two week course of primaquine on return from PNG would not be expected to affect the incidence of falciparum malaria but would be expected to reduce the incidence of vivax malaria after cessation of chemoprophylaxis. The importance of primaquine in this respect cannot be assessed from this study. One soldier developed vivax malaria almost six months after return from PNG despite taking a full course of chemoprophylaxis and a two week course of primaquine, thus illustrating the resistance of the hypnozoites of the Chesson strain of *P. vivax* to ablative therapy with primaquine and the requirement to consider vivax malaria as a potential problem during this period.

**Conclusion**

This study showed that the addition of maloprim to a proguanil-chloroquine combination for malaria chemoprophylaxis in PNG caused an overall reduction in the incidence of malaria and significantly reduced the risk of acquiring falciparum malaria.

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