

MALARIA PROPHYLAXIS/RADICAL CURE : RECENT EXPERIENCES OF THE AUSTRALIAN DEFENCE FORCE

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ABSTRACT • Since the eighties, the Australian Defence Force has deployed soldiers in malaria-endemic areas: Cambodia, Somalia, Rwanda, Bougainville, and East Timor. Currently, doxycycline is used as first line prophylactic drug and mefloquine is recommended for those who cannot tolerate the antibiotic. In 1998, the Australian Defence Force participated in the evaluation of tafenoquine for prophylaxis of both *falciparum* and *vivax* malaria in Thai soldiers. At the completion of this six-month study, 29 of 205 soldiers had come down with malaria including eight with *falciparum* malaria, 20 with *vivax* malaria, and one with mixed infection. A total of 28 of the 101 soldiers in the placebo group were infected with malaria as compared with only one of the 104 soldiers in the tafenoquine group. In 1999, another study was started on the island of Bougainville to compare the effectiveness a 3-day course of tafenoquine and a 14-day course of primaquine for radical cure of *vivax* malaria. At the present time, 411 soldiers have completed the study including 201 in tafenoquine arm and 210 in primaquine arm. Seven soldiers in each arm developed *vivax* malaria after returning to Australia. These results indicate that tafenoquine is not superior to primaquine in preventing *vivax* malaria. However study participants preferred the shorter course using tafenoquine and operationally it was found to be more suitable than primaquine.

KEY WORDS • Malaria - Australia - Bougainville - Thailand - Chemoprophylaxis - Tafenoquine - Doxycycline - Mefloquine.

L'EXPERIENCE RECENTE DE L'ARMEE AUSTRALIENNE DANS LA CHIMIOPROPHYLAXIE ET LA CURE RADICALE DU PALUDISME

RESUME • Depuis les années quatre-vingts, l'armée australienne a déployé des troupes dans des régions d'endémie palustre : Cambodge, Somalie, Timor Oriental. Actuellement, la doxycycline est utilisée comme antipaludique de première ligne et la méfloquine pour ceux qui ne tolèrent pas la doxycycline. En 1998, l'armée australienne a participé à l'évaluation chez des soldats thaïlandais de la tafénoquine en prophylaxie du paludisme à *Plasmodium falciparum* et *Plasmodium vivax*. A la fin de l'étude qui a duré six mois, 29 soldats sur 205 ont eu un accès palustre : 8 à *Plasmodium falciparum*, 20 à *Plasmodium vivax* et une infection mixte. Dans le groupe placebo, 28 soldats sur 101 ont eu un accès palustre. Dans le groupe tafénoquine, seulement un soldat sur 104 a eu un accès palustre à *Plasmodium vivax*. En 1999 une autre étude a été entreprise sur l'île de Bougainville pour comparer l'efficacité en cure radicale d'un traitement de 3 jours sous tafénoquine et d'un traitement de 14 jours sous primaquine. A ce jour, un total de 411 soldats a été inclus : 201 dans le groupe sous tafénoquine et 210 dans le groupe sous primaquine. Sept soldats dans chaque bras ont développé un paludisme à *Plasmodium vivax* après leur retour en Australie. Ces résultats indiquent que la tafénoquine n'est pas supérieure à la primaquine dans la prévention du paludisme à *Plasmodium vivax*, mais les participants à l'étude ont préféré les schémas thérapeutiques courts par tafénoquine.

MOTS-CLES • Paludisme - Australie - Bougainville - Thaïlande - Chimio prophylaxie - Tafénoquine - Doxycycline - Méfloquine.

BACKGROUND

PROPHYLAXIS IN THE AUSTRALIAN DEFENCE FORCE

Over the past two decades the Australian Defence Force (ADF) has deployed personnel on peace-enforcement and - monitoring duties in areas where malaria is endemic such as Cambodia, Somalia, and more recently East Timor. The ADF uses chemoprophylaxis and personal protection measures to protect its personnel from malaria infections. The increasing spread of multidrug-resistant *Plasmodium falciparum* malaria has led to an urgent need for new prophylactic

drugs and, as part of this effort, the ADF is highly supportive of evaluating prophylactic agents, particularly those with novel modes of action. Currently for malaria prophylaxis, the ADF uses doxycycline as its first line prophylactic drug and for those who cannot tolerate the antibiotic, mefloquine is recommended.

Both drugs are considered the most effective malaria chemoprophylactic agents available today. Mefloquine has a long half-life suitable for weekly prophylaxis, which makes the drug very attractive for military personnel. Although the side-effects of mefloquine, such as nausea and headaches, are usually mild and do not affect the activities of subjects, more worrying is mefloquine's association with serious neuropsychiatric symptoms in about 1 of 10,000-20,000 subjects taking the drug. The occurrence of neurologic side-effects, particularly dizziness, has led to the concern that mefloquine may impair performance and precision while using military equipment and weapons. It is the concern of neurological

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reactions associated with mefloquine that doxycycline is the first drug of choice for the ADF.

Doxycycline is strongly recommended in areas of mefloquine-resistant *falciparum* malaria, such as the Thai-Cambodian border, and resistance to the antibiotic has not yet been documented. Other benefits of doxycycline is that it is a lower-cost alternative to mefloquine and it might possess causal prophylactic activity in eliminating pre-erythrocytic liver forms of malaria and thus allowing subjects to stop prophylaxis 14 days after leaving a malarious area. Although doxycycline is highly effective if taken as recommended, daily dosing may decrease compliance. Gastrointestinal disturbances and photosensitivity reactions are the main side-effects of doxycycline, and these are usually mild and self-limiting.

Evaluation of tafenoquine for prophylaxis.

Although the ADF has found doxycycline to be an effective prophylactic drug, it is well accepted that no prophylactic agent is 100 % effective. Since the effectiveness and tolerability of chemoprophylactic drugs are of concern to the ADF, and realizing that resistance will eventually develop to all commonly used drugs, the ADF is keen to evaluate new drugs in some of the worst malarious areas in the world. Recently, in support of this effort, the ADF has participated in the evaluation of the new antimalarial drug, tafenoquine, for prophylaxis against both *falciparum* and *vivax* malaria.

Tafenoquine is a primaquine analogue, is active against all stages of the malaria parasite, and is jointly being developed by the US Army and SmithKline Pharmaceuticals. Animal and *in vitro* studies have demonstrated tafenoquine to be more active than primaquine. Compared with primaquine, tafenoquine has a longer half-life (14 days *versus* 6 hours) which makes it a highly suitable drug for either prophylaxis or short-term treatment for radical cure of *vivax* malaria.

In 1998, the ADF's Army Malaria Institute (AMI) collaborated with the US and Thai Components of the Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, in the evaluation of the effectiveness of tafenoquine in Thai soldiers located in area where both *Plasmodium falciparum* and *Plasmodium vivax* malaria is prevalent. The primary aim of the tafenoquine study was to compare the extent of protection against malaria infections of a three day loading dose regimen of tafenoquine (400mg base x 3 days) followed by monthly tafenoquine (400mg) *versus* placebo in Thai soldiers deployed on duty along the Thai-Cambodian border. The rationale behind the monthly regime was based on the lengthy half-life of tafenoquine and the observation from an earlier study in Kenya (G.D. Shanks, personal communication, 1997) that showed volunteers who only received the loading dose of tafenoquine (400mg x 3 days) were protected from *falciparum* malaria for up to 80 days post-dose.

Two hundred and five Thai soldiers were invited to participate in the trial and informed consent was obtained from each volunteer. The study was ethically approved by the Scientific and Ethical Review Committees of the Royal Thai Army and the US Army, and the Australian Defence Medical Ethics Committee. The Thai soldiers were randomized to receive either tafenoquine or placebo capsules.

Randomization resulted in 104 soldiers receiving tafenoquine and 101 soldiers receiving placebo. The trial commenced in late March 1998 with initial blood screening of the soldiers to determine their suitability to participate in the study. Those soldiers who passed the selection criteria were given presumptive treatment of artesunate plus doxycycline in April 1998 to remove any pre-existing malaria infections prior to receiving the loading dose of tafenoquine or placebo. Blood smears for monitoring the development of malaria infections in the soldiers were collected weekly from each volunteer and safety profiles of blood chemistries were done monthly. Blood collections for drug analysis were collected randomly from each volunteer throughout the trial period. The last monthly dose of either tafenoquine or placebo was administered in late August 1998 and follow-up of the soldiers in a non-malarious area continued for a further month (until late October 1998).

At the completion of the study, 29 soldiers had come down with malaria infections. Of these, eight had *falciparum* malaria, 20 had *vivax* malaria and one soldier had a mixed infection. In the placebo group, 28 soldiers were infected with malaria over the six months of the study period and only one soldier with *vivax* malaria was on tafenoquine. The latter soldier had a plasma tafenoquine concentration of about 2-fold less than those soldiers treated with tafenoquine who were not infected with malaria. Thus, in this study 99 % (103 of 104) of the Thai soldiers on tafenoquine were protected from malaria infections. The drug was well tolerated with only self-limiting side effects such as nausea and mild diarrhoea being reported in both the tafenoquine and placebo groups. A few cases of vomiting were also noted.

One of the objectives of the Royal Thai Army study was to determine the population kinetics of tafenoquine in Thai soldiers after receiving the monthly regimen. The mean age and weight of the 104 volunteers on tafenoquine were 28.9 years (range 21-46 years) and 60.3 kg (range 45-90 kg). During the study period, blood samples were collected randomly in the field from the volunteers, two to three times each month. Plasma tafenoquine concentrations were measured by reversed-phase high-performance liquid chromatography, with fluorescence detection. The population pharmacokinetics of tafenoquine was estimated using a nonlinear mixed effects modelling program (NONMEM). A one-compartment model with first-order absorption and elimination was found to best characterize the plasma tafenoquine concentration data. The population estimates of clearance was 3.20 L/hr, while the typical apparent volume of distribution for tafenoquine was 1820 L for subjects having the population average age and weight. These kinetic estimates indicate that tafenoquine is slowly cleared from the body and it accumulates in tissue compartments. The elimination half-life of tafenoquine in the Thai subjects was 16.0 days.

Evaluation of tafenoquine for radical cure.

Vivax malaria continues to be a major problem for ADF personnel after returning to Australia. This is because hypnozoites can remain dormant in the liver for weeks, months or even years after acquiring the original infection and

because prophylactic drugs such as doxycycline and mefloquine are capable of only eliminating parasites after they are released from the liver into the blood stream. Since the 14-day primaquine eradication course is the only way of eliminating residual liver parasites and in certain areas it is becoming less and less effective, the ADF was rather anxious to assess the potential value of a 3-day course of tafenoquine in preventing *vivax* malaria. Because of tafenoquine's greater antimalarial activity and longer half-life, it was generally anticipated that it would be superior to primaquine in eliminating the liver parasites.

The standard primaquine eradication course for *vivax* malaria is a daily dose of 15 mg base for 14 days. Because more than 30 % of *vivax* infections acquired in the Southwest Pacific area are not cured by this regimen, the daily adult dose of primaquine used by ADF personnel was increased to 22.5 mg base daily (7.5 mg three times a day) for 14 days about 30 years ago. The ADF has maintained this dose regime reserving the higher 30 mg primaquine daily treatment course for established treatment failures.

The higher dose of primaquine has been increasingly less effective in preventing or curing *vivax* malaria in the Southwest Pacific area. As far back as 1989, 20-25 % of Australian soldiers developed malaria after returning to Australia following 3-4 week training exercises in Papua New Guinea (PNG). Some of these breakthroughs are due to primaquine-refractory parasites (Chesson strain) and others are due to inadequate compliance with the cumbersome 14-day eradication regimen. Recent experience on the island of Bougainville and other areas of PNG suggests that the ineffectiveness of the primaquine course remains a major health problem after the return of ADF personnel from malarious areas of the Southwest Pacific region. Chemoprophylaxis with doxycycline is able to suppress and prevent both *falciparum* and *vivax* malaria during their stay in PNG. But the hypnozoites (liver stages of *Plasmodium vivax*) are not being eliminated by the current primaquine eradication course probably because of either drug compliance problems after soldiers return to Australia, or the presence of primaquine tolerant parasites.

In January 1999, AMI initiated a trial to compare the effectiveness and tolerability of tafenoquine and primaquine in preventing *vivax* malaria in Australian soldiers returning back to Australia after serving 2-4 months on the island of Bougainville. Malaria is one of the most serious diseases on Bougainville and is responsible for high mortality and morbidity in the local population. Of those Bougainvilleans reporting to the various health clinics on the island, with fever type symptoms, about half are carrying malaria parasites.

Falciparum malaria is the predominant species, accounting for 70 %-80 % of the infections, followed by *vivax* malaria. As ADF personnel are located in close proximity to the local populations, particularly the field teams, they are continuously being exposed to malaria during their deployment.

The trial is still ongoing but so far, 411 soldiers have completed the tafenoquine versus primaquine study, with 201 on tafenoquine and 210 on primaquine. Of these volunteers, seven in the tafenoquine group and seven in the primaquine group have subsequently developed *vivax* malaria after returning to Australia. *Vivax* malaria was diagnosed in the tafenoquine failures at weeks 13-20, and in the primaquine failures at weeks 8-21.

The results so far indicate that tafenoquine is no more superior to primaquine in preventing *vivax* attacks in ADF personnel returning from Bougainville. Although this finding is disappointing, the participants in the study preferred the short course of tafenoquine over the lengthy and cumbersome primaquine regime. Furthermore, because tafenoquine is effective against *falciparum* malaria, the soldiers on tafenoquine did not have to take doxycycline for 14 days after returning home to Australia.

After reviewing the results from Bougainville and elsewhere, there is a need for further studies to be carried out to determine whether tafenoquine can be used more effectively if it is given before malaria exposure, thereby preventing liver cells from becoming infected. Based on clinical prophylactic trials with daily primaquine by the US Navy (NAMRU-2) in Irian Jaya and tafenoquine in Thailand, it is quite likely that weekly prophylaxis with tafenoquine could prevent malaria infections and obviate the need for a terminal eradication course after leaving a malarious area such as Bougainville or East Timor. This would obviously have significant operational advantages. AMI is planning to participate in a multi-centre Phase III trial of tafenoquine for weekly prophylaxis in ADF personnel deployed to East Timor.

CONCLUSIONS

The ADF's involvement in the two tafenoquine trials reinforces the importance and value of collaboration between armies that share the common desire to provide its military personnel with the best protection measures against malaria infections. A concerted effort needs to be made to protect soldiers from malaria as this disease has and continues to pose the greatest health threat to military forces into the new millennium.