The challenge of effective chemoprophylaxis against malaria

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THE CHEMOPROPHYLAXIS of malaria has become complex because of increasing resistance of *Plasmodium falciparum* to various drugs and adverse reactions associated with them. From a military perspective, peace enforcement and peace keeping activities have recently seen personnel from various armies deployed to areas of the world where malaria is endemic. Over the past two decades the Australian Defence Force (ADF) has deployed personnel to malarious countries such as Bougainville, New Guinea, Cambodia, Somalia, Rwanda and East Timor. Due to the emergence and spread of multidrug-resistant *P. falciparum* parasites, the armamentarium of effective prophylactic drugs has shrunk considerably. In addressing the urgent need for improved malaria prophylaxis, the ADF has been in the forefront of assessing the effectiveness of new drugs and drug regimens.

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Synopsis

- Malaria has adversely affected the operational effectiveness of military forces throughout recorded history. Resistance to current antimalarial drugs is increasing at an alarming rate and is now present in many tropical areas where military personnel are deployed.
- Doxycycline and mefloquine are currently the drugs of choice for malaria prophylaxis, but new prophylactic agents are urgently needed to address problems with efficacy, tolerance and compliance.
- The introduction of Malarone (a combination of atovaquone and proguanil hydrochloride) for the treatment of malaria has raised the possibility that this drug may also be used in malaria prophylaxis.
- Since none of the abovementioned drugs are able to prevent vivax malaria when they are no longer taken following departure from a malarious area, terminal prophylaxis or "eradication" with primaquine is still required.
- Tafenoquine, a primaquine analogue, is a new drug that is active against all stages of the malaria parasite. It is more effective and longer acting than primaquine. Clinical trials have shown tafenoquine to be a promising drug for treating vivax malaria and preventing malaria infections.
- The ADF is assessing the effectiveness of tafenoquine and, if it can be shown to be effective and safe in the prevention of malaria, the ADF will be able to provide its personnel with better protection against malaria.

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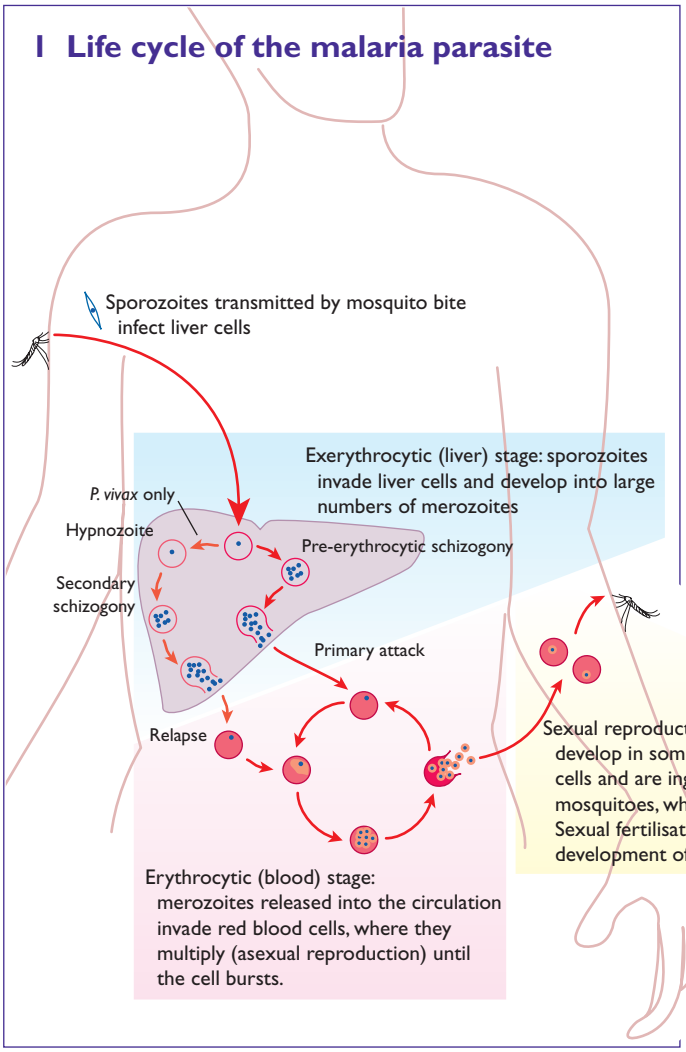
Current chemoprophylaxis

Doxycycline is the first line prophylactic drug used by the ADF for malaria prophylaxis.[1] Mefloquine is also an effective prophylactic drug[2] and is used when military personnel are unable to take doxycycline for any reason. Both drugs act against the asexual blood stages of the parasite and are generally considered to be the most effective agents available today for malaria chemoprophylaxis.[3,4]

Doxycycline is recommended for areas with mefloquine-resistant falciparum malaria, such as the Thai–Cambodian border, and resistance to the antibiotic has not yet been documented. Other benefits of doxycycline are that it is a lower-cost alternative to mefloquine and that it might possess causal prophylactic activity and act against the pre-erythrocytic stages



of falciparum malaria in the liver. It is also effective against some gram-positive and gram-negative microorganisms. Although doxycycline is highly effective if taken as recommended, inadequate compliance with the daily prophylactic dose can result in malaria breakthroughs. Side-effects include nausea, abdominal cramps, oesophagitis, photosensitivity and superinfection.

Mefloquine has a pharmacological half-life of two to three weeks, which means that the drug can be taken only once a week. The incidence of side effects to mefloquine is comparable to that of other commonly used prophylactic drugs such as doxycycline and chloroquine plus proguanil.[5] Nausea, dizziness and headaches are usually mild and do not interfere significantly with daily activities. However, rarely, mefloquine can cause serious neuropsychiatric disturbances such as seizures, psychosis and nightmares (reported to affect about 1 in 10 000 individuals on prophylaxis).[6] The occurrence of neurological side effects, particularly dizziness, has led to concern that mefloquine may impair the performance and precision of military personnel using weapons and military equipment.

Possible alternative to doxycycline — Malarone

Although the ADF has found doxycycline to be an effective prophylactic drug, it cannot be taken by everyone and, under certain operational conditions, compliance is a problem. Malarone, a combination of atovaquone and proguanil, is a possible alternative to doxycycline.[7] This drug combination has been registered in Australia for the treatment of malaria and has been licensed for malaria chemoprophylaxis in some other countries, including the USA. Preliminary observations in ADF personnel deployed to Bougainville have shown that daily prophylaxis with Malarone and doxycycline protected all participating volunteers against malaria while they were on chemoprophylaxis. Malarone was also tolerated as well as or better than doxycycline. The findings indicate that Malarone may become a very useful alternative to doxycyline for protecting ADF personnel against malaria during their deployment to endemic areas.

Primaquine for terminal prophylaxis (eradication) of vivax malaria

Doxycycline, mefloquine and Malarone are unable to prevent acute attacks of vivax malaria after the return of ADF personnel to Australia because none of these drugs has any effect on the persistent liver stages (or hypnozoites) of *P. vivax*. Primaquine is the only drug currently available for eliminating these liver stages and preventing vivax malaria after discontinuing malaria prophylaxis. However, an increasing number of vivax infections acquired in the South Pacific area are no longer being eradicated by primaquine.[1] The drug also has a low therapeutic index and can cause haemolysis in glucose-6-phosphate dehydrogenase deficient individuals. Furthermore, mild gastrointestinal disturbances and methaemoglobinaemia are common. Primaquine has a short half-life (4–6 hours) and has to be taken at least once a day for 14 days. A standard course for Papua New Guinea, the Solomons, Indonesia and East Timor is 15 mg twice a day. As might be expected, incomplete compliance with this cumbersome regimen sometimes results in persistent vivax infection.

Tafenoquine — a new primaquine analogue

Tafenoquine (8-[(4-amino-1-methylbutyl) amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoro-methyl-phenoxy) quinoline, succinate), also known as WR 238605 or Etaquine, is a new 8-aminoquinoline antimalarial drug that has been developed over the past decade by the Walter Reed Army Institute of Research (WRAIR) in the USA. It is a primaquine analogue that was developed initially in the search for a safer, more effective and longer-acting replacement for primaquine. Further studies have revealed that, in addition to its action against

the liver stages, tafenoquine is also a blood schizontocide active against the asexual blood stages of the parasite.

Pre-clinical trials

In animal studies tafenoquine has demonstrated activity against both blood and liver stages of malaria.[8] It is 4–100-fold more active than primaquine against the blood stages of *P. berghei* in rodents and about 7 times more effective than primaquine against the liver stages of *P. cynomolgi* in rhesus monkeys.[9] The observed blood schizontocidal activity of tafenoquine has also been demonstrated against a chloroquine-resistant strain of *P. vivax* (AMRU-1) adapted to *Aotus* monkeys.[10] This *in vivo* antimalarial activity has been further confirmed *in vitro* against isolates of *P. falciparum* malaria of varying levels of drug resistance.[11] On an equimolar basis, tafenoquine was found to be four times more active than primaquine against chloroquine-sensitive clones, and 15 times more active against resistant clones. Animal and *in vitro* studies designed to evaluate gametocytocidal and sporontocidal activities have suggested that tafenoquine has a potential role in blocking malaria transmission.[12]

Pharmacokinetic properties

Pharmacokinetic data for tafenoquine have been derived from values obtained after oral administration of the drug.[13,14] In human studies, tafenoquine has been shown to be well absorbed from the gastrointestinal tract and peak blood levels occur around 12 hours after oral administration. Preliminary data suggest that co-administering tafenoquine with a meal increases bioavailability by 30% compared with administration on an empty stomach (Brueckner RP, unpublished data). After systemic absorption, the drug decays with a monoexponential elimination half-life of 10–14 days. The apparent volume of distribution of tafenoquine has been estimated at about 2550 L, which indicates that tafenoquine is distributed extensively in the tissues. Metabolic studies in beagle dogs and rhesus monkeys have shown tafenoquine to be metabolised slowly.[15] The drug is eliminated primarily in the bile and faeces with enterohepatic recirculation. Tafenoquine is highly plasma protein bound (96%–99%). Whole blood concentrations are about 1.8 times greater than plasma concentrations, indicating that tafenoquine accumulates inside red cells.

Clinical studies

Rising, single oral-dose safety and tolerance studies in healthy volunteers receiving doses of 4–600 mg base of tafenoquine were generally well tolerated.[14] The main symptoms were mild headaches and gastrointestinal disturbances. During this phase of the investigations it was noted that a single oral dose of 600 mg tafenoquine given a day before challenge with mosquitoes infected with *P. falciparum* successfully protected three of four non-immune individuals.[13] The fourth volunteer developed malaria on day 31, compared with day 10 in placebo controls.

Major Bob Cooper feeding mosquitoes to assess effectiveness of new repellents.

Blood tafenoquine concentrations in this individual were half those observed in the protected volunteers.

Because of this encouraging result, multiple-dose safety and tolerance studies were initiated in healthy volunteers. Administration of oral doses of 200, 400 and 600 mg/week for 10 consecutive weeks revealed mild dose-dependent gastrointestinal disturbances (nausea, vomiting, diarrhoea), headache, light-headedness and dysgeusia (Brueckner RP, unpublished data). While all three regimens were safe, the highest dose (600 mg/week) was not considered suitable for prophylaxis due to the frequency of gastrointestinal symptoms.

This led to the first prophylactic efficacy study, in 1997, during which weekly doses of 200 mg and 400 mg tafenoquine were investigated in 238 semi-immune adult volunteers in Kenya.[16] Both drug regimens were well tolerated and they prevented the development of *P. falciparum* infections in 88% of the participants living in a highly endemic area of Kenya. An important observation in this trial was that a short-term course of tafenoquine (400 mg daily for three days) provided 91% protective efficacy for seven weeks after drug administration. Two further studies in Africa confirmed the value of tafenoquine as a prophylactic drug against falciparum malaria.[17,18]

In 1998, a placebo-controlled study was carried out in Thailand to assess the prophylactic efficacy of tafenoquine against both falciparum and vivax malaria.[19] Over 200 non-immune Thai soldiers stationed on the Thai–Cambodian border were given a daily dose of 400 mg tafenoquine for three days, followed by a monthly dose of 400 mg tafenoquine for five months. Only one vivax infection was observed in the tafenoquine group, whereas 20 vivax, eight falciparum and one mixed infection occurred in the placebo group.

In addition to the prophylactic studies, the value of tafenoquine in preventing relapses was assessed in Thai patients

infected with vivax malaria.[20] After initial treatment with chloroquine, patients received three different doses of tafenoquine: a single dose of 500 mg; 300 mg daily for seven days; or 500 mg daily for three days followed by the same regimen one week later. A fourth group of patients received chloroquine only. Patients were followed for 2–6 months after treatment to document any relapses of vivax malaria. In the 35 patients receiving tafenoquine, two (5.7%) were observed to have a relapse, whereas four (44.4%) of the nine patients receiving chloroquine had a relapse of vivax malaria. Side effects with tafenoquine were generally mild, sporadic, and transient, consisting predominantly of headaches and gastrointestinal disturbances.

It has been well documented that primaquine can cause serious haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals.[21] Tafenoquine, a synthetic analogue of primaquine, may also produce haemolysis in G6PD-deficient individuals. Studies are currently underway to determine the safety of tafenoquine in these individuals. Until these studies are completed, all recipients of tafenoquine have to be screened for this enzyme deficiency before receiving the drug.

Evaluation of tafenoquine in ADF personnel

The encouraging results obtained in Thailand prompted the Army Malaria Institute (AMI) to initiate a study with this drug in ADF personnel deployed to Bougainville. Volunteers were given 400 mg daily for three days just before returning to Australia and the effectiveness of this regimen was compared with the standard 14-day primaquine eradication course. The short three-day tafenoquine regimen was certainly more popular than the much longer primaquine course and compliance was good. Results of these investigations are still being evaluated, but preliminary findings suggest that this drug is not entirely effective in preventing vivax malaria following deployment to areas such as Bougainville, where persistent liver stages (or "hypnozoites") of *P. vivax* are relatively refractory to primaquine.

Since tafenoquine may have greater activity against the pre-erythrocytic liver stages of *P. vivax*, further studies are being planned to investigate the value of this drug as a prophylactic agent during the period of exposure to malaria-infected mosquitoes (rather than only at the end of deployment overseas). Based on clinical and pharmacokinetic data, a tafenoquine regimen consisting of a loading dose (200 mg for three days) followed by 200 mg weekly has been selected for assessing the effectiveness of tafenoquine in protecting larger population groups against malaria. The Australian Defence Force Medical Ethics Committee has approved the proposal that ADF personnel deployed to East Timor be given the opportunity to participate in a large-scale prophylactic study during 2000–2001. Presently, a randomised, double-blind comparative trial of tafenoquine and mefloquine is being conducted in the First Battalion of the Royal Australian Regiment (1RAR) in East Timor. The study is a collaborative effort between GlaxoSmithKline Pharmaceuticals, the US Army and the AMI.

Dr Nanhua Chen using DNA technology to detect drug resistant malaria

The importance of assessing the value of tafenoquine in Australian military personnel cannot be overstated. For the first time in history, there is a drug that seems to provide complete protection against all types of malaria and which may interrupt malaria transmission.[22] Although non-immune short-term travellers visiting malarious areas can ultimately provide some information about the efficacy of this drug, there is no substitute for assessing its effectiveness in ADF personnel who are operating under field conditions and are being exposed to malaria strains peculiar to areas of particular strategic interest to Australia. By participating in the early evaluation of this novel drug, the ADF will hopefully be able to protect its personnel much more effectively against the ravages of malaria. It should then also be in a position to point the way for military personnel of other armies to be protected

Mr Wayne Lyons measuring serum drug levels in samples from volunteers in prophylactic study.

more effectively against malaria, and thereby reduce the continuing health threat of this potentially lethal disease to military forces.

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Book review

Neurosurgery in the tropics

Geoffrey V Rosenfeld and David A K Watters. ***Neurosurgery in the tropics. A practical approach to common problems.***
Melbourne: Macmillan Education, 2000. $63. ISBN 0 33 68412 5

MANY WHO PRACTISE MEDICINE outside major centres are confronted with inescapable patient management decisions with potential neurological consequences. Not all neurosurgery can be conducted by full-time neurosurgeons. This new book is a practical guide for doctors operating outside centres with a practising neurosurgeon, written by authors with extensive experience under difficult circumstances in Australia, Papua New Guinea, Zimbabwe, Zambia and other developing countries. It is a splendid, clearly written diagnostic guide for those in the field. It covers the crucial questions of clinical assessment in the potential neurosurgical context, and will be an aid for those who have to decide on aeromedical evacuations, summoning of trauma teams or (most difficult of all) when not to operate.

The book describes details of common neurosurgical operations, particularly emergency operations to preserve life or brain function, in the clearest terms. There are excellent sections on head injury in the context of developing countries, congenital malformations involving the craneospinal axis, diagnosis of brain death, neurorehabilitation and medicolegal issues.

I commend the book to all who work in tropical settings, refugee camps, or in outback or other isolated medical practices, and to all those doctors who may go on operational deployments with the Defence Health Service.

Major General John Pearn, AM, RFD (Rtd)