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Malaria prevention in the expatriate and long-term traveller

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SYNOPSIS

The prevention of malaria in expatriates and long-term travellers is complex. The traveller's doctor needs to consider the destination, the nature of the travel, the effectiveness and potential adverse effects of antimalarial medication, and the general health of the traveller. A preventative regimen can be devised combining several strategies including mosquito avoidance measures, chemoprophylaxis, emergency standby treatment and rapid self-diagnosis of malaria.

Index words: chemoprophylaxis, chloroquine, doxycycline, mefloquine.

(*Aust Prescr* 2002;25:66–9)

Introduction

In 1999, 3.2 million Australians travelled abroad, and travel to countries where malaria is endemic is becoming increasingly common. Each year an estimated 30 000 cases of malaria occur in non-immune travellers worldwide.¹ Many people, including aid workers, missionaries, students and healthcare workers, are travelling to work and live in rural and remote malarial regions. The estimated mortality rate for falciparum malaria in non-immune adults is up to 5%, so the medical practitioner entrusted with providing safe and suitable travel health advice will need to carefully consider the need for antimalarial prophylaxis. When the traveller's stay in an endemic area exceeds six months the issues can become quite complex.

Issues to consider

There is no perfect choice of antimalarial regimen for long-term travellers and expatriates. Prevention involves careful consideration of a number of factors, which include:

- the prevalent endemic malarial species – prophylaxis needs to be seriously considered for travel to areas with significant levels of *Plasmodium falciparum* because of its associated mortality
- the susceptibility of malarial parasites to commonly used drugs – endemic chloroquine-resistant *P. falciparum* reduces the effectiveness of chloroquine-based regimens
- the intensity of malaria transmission – the higher the intensity, the greater the need for antimalarial prophylaxis
- the risk of exposure – includes issues such as urban or rural residence, the type of accommodation and the proximity of mosquito breeding grounds

- the duration of stay – the longer one stays the greater the cumulative risk of contracting malaria, but also the greater the problems of compliance and adverse effects
- the seasonal pattern – if transmission is seasonal, prophylaxis may only be required during the malarial season
- the availability of reliable diagnostic tests and medical care for malaria – if these are lacking malaria poses a greater health risk and so there is a greater need for prophylaxis
- the potential adverse effects of the prophylactic medications – may affect their suitability for the individual traveller
- compliance issues – these need to be considered as the traveller may be better served by a less effective regimen that can be adhered to, than a more effective regimen that cannot
- the traveller's characteristics – factors such as age, pregnancy, comorbidities and drug allergies all have a significant bearing on the choice of prophylaxis
- the traveller's preference – this needs to be strongly considered as it has a vital bearing on the ultimate success of any prophylactic regimen.

These issues need to be discussed openly with the traveller. A mutually acceptable plan for malaria prevention can then be developed.

Malarial protective measures

Protection against malaria in the long-term traveller can include some or all of the following:

- mosquito avoidance measures
- chemoprophylaxis
- emergency standby treatment
- self-diagnosis kits.

Mosquito avoidance measures

These measures are the mainstay of any long-term antimalarial prophylaxis regimen. They are important in reducing the risk of contracting malaria in any traveller, but because of the many difficulties and limitations of chemoprophylaxis they are vital in long-term travellers. Adequate time must be spent with the patient to educate them about measures to reduce:

- exposure to the female *Anopheles* mosquito (minimise outdoors activities during its feeding time from dusk to dawn, and protect living quarters from mosquitoes)

- attracting the mosquito (avoid dark clothing, aftershaves, perfumes)
- bites (covering exposed skin areas with clothes or diethyltoluamide (DEET)-containing repellents, use of mosquito nets, permethrin impregnated clothes and nets, and using insecticides or repellents inside dwellings).

Chemoprophylaxis

The currently available medications we feel should be considered are summarised in Table 1.

Doxycycline

Doxycycline is very effective prophylaxis for chloroquine-resistant *P. falciparum*. There are no known serious adverse events from its long-term use, however daily dosing is a disadvantage and may lead to poor compliance. Vaginal thrush and photosensitivity may be troublesome adverse effects. It should be swallowed with food or an adequate quantity of water to avoid oesophagitis. An advantage of doxycycline is that it may provide some protection against infectious diarrhoea, tick-borne infections, scrub typhus, leptospirosis and some sexually transmitted diseases such as chlamydia. It is contraindicated in pregnant or breastfeeding women and children under eight years of age.

Mefloquine

Mefloquine has been extensively used and is very effective prophylaxis for people living in areas where chloroquine-resistant *P. falciparum* is endemic. Weekly administration helps compliance, and there has been no increase in adverse events with long-term use.² In prophylactic doses it is generally well tolerated with studies showing no significant differences in adverse events compared to other antimalarial regimens apart from atovaquone/proguanil.² Although severe neuropsychiatric adverse events are rare (estimated 1:10 000 users), it is not recommended for those who have underlying neuropsychological problems (e.g. epilepsy, depression). Some people experience mild neuropsychological effects such as headache, dizziness, mood changes, insomnia and vivid nightmares. As most adverse effects will occur within the first month of use, a trial of mefloquine for 3–4 weeks before

departure to test its tolerability in long-term travellers is often worthwhile. We do not recommend mefloquine in the first trimester of pregnancy unless there is a significant risk of chloroquine-resistant *P. falciparum* malaria, although there is mounting evidence to support its safety. It is also not recommended for children less than 5 kg in weight.

Atovaquone/proguanil hydrochloride

This combination is highly effective prophylaxis for chloroquine-resistant falciparum malaria. Although gastrointestinal symptoms can occur it is well tolerated, and comparative studies show it to be better tolerated than mefloquine, doxycycline and chloroquine/proguanil for prophylaxis.¹ The use of the combination by long-term travellers is limited by its expense, a lack of long-term safety data and concerns about the development of resistance. We therefore currently do not routinely recommend its use for prophylaxis.

Chloroquine

Chloroquine has the advantage of improved compliance because it is taken weekly. It can be used by pregnant women and young children and is generally well tolerated. The main adverse effects are gastrointestinal upsets and a bitter taste. Long-term use is safe, however regular retinal screening is recommended after five years of continuous use as there is a potential risk of cumulative retinal toxicity. Chloroquine reduces the effectiveness of intradermal rabies vaccine necessitating vaccination by the intramuscular route.

The use of chloroquine is limited by the resistance of *P. falciparum* parasites. It may still have a role, taken alone or combined with proguanil, in areas with low resistance rates or low transmission risk (e.g. India) or where medical care is readily accessible. Chloroquine may also be used if the patient is intolerant of or reluctant to take other regimens or will have problems with compliance.

Proguanil

The use of proguanil is limited by the widespread resistance of *P. falciparum* parasites, and lack of compliance with its daily dosing. It is mainly used in combination with chloroquine.

Table 1

Characteristics of recommended antimalarial prophylactic medications

Medication	Resistance*	Dose	Frequency	Pregnancy	Children	Time prior to entering a malarial endemic area	Time after leaving a malarial endemic area
Chloroquine	Yes	300 mg	weekly	Yes	Yes	1 week	4 weeks
Doxycycline	No	100 mg	daily	No	≥ 8 years	2 days	4 weeks
Mefloquine	Yes †	250 mg	weekly	No ‡	> 5 kg	2 weeks	4 weeks
Proguanil	Yes	200 mg	daily	Yes	Yes	1 day	4 weeks
Atovaquone/proguanil	No	250 mg/ 100 mg	daily	No	> 11 kg	1 day	1 week

* for falciparum malaria

† resistance reported in Northern Thailand, Cambodia and Myanmar

‡ may be used in 2nd and 3rd trimesters

Long-term use is safe, but there is a low incidence of adverse effects (mouth ulcers). It can be used in pregnancy and childhood.

Emergency standby treatment (Table 2)

Long-term travellers may choose not to take chemoprophylaxis, but instead rely on mosquito avoidance measures and the use of a reliable treatment if they become infected. If symptoms suggestive of malaria develop, they either seek urgent medical attention, if available within 24 hours, or take an emergency self-treatment course effective for the local malarial resistance patterns, preferably after using a self-diagnosis malarial kit. For standby treatment to be an option, the traveller needs to be well educated about the various symptoms that suggest malarial infection, and be precisely instructed on how to take the treatment. Self-treatment should always be followed by a medical consultation as soon as possible.

Atovaquone/proguanil hydrochloride

This regimen is highly effective for all forms of malaria, there is no reported resistance and adverse effects are minimal. The combination can be used after any of the chemoprophylactic drugs. Its major disadvantage is that it is significantly more expensive than other regimens.

Mefloquine

This is an effective treatment in areas without reported resistance. A disadvantage is the high risk of adverse reactions (28–59%) associated with a treatment course.³ There are rare reports of severe neurological disturbances such as depression, psychosis and seizures.⁴ Emergency treatment with mefloquine is not recommended for people taking mefloquine for prophylaxis as there is an increased risk of adverse events.

Sulphadoxine-pyrimethamine

This offers a simple, inexpensive and well-tolerated regimen. However, it is no longer recommended in Africa, South America and South-East Asia because of increasing resistance. Uncommon, but serious, complications such as Stevens-Johnson syndrome and agranulocytosis, further limit its use.

Quinine

This is highly effective against chloroquine-resistant malaria. However, its use is limited by a high incidence of adverse effects, and a complex, prolonged regimen requiring combination with another drug.

Halofantrine

This is an effective treatment which is active against chloroquine-resistant *P. falciparum*. It is available via the Special Access Scheme, however, we do not recommend it because of its potential for fatal cardiac arrhythmias (especially in those on mefloquine chemoprophylaxis) and the availability of safer, effective alternative drugs.

Self-diagnosis kits

Relatively inexpensive kits (e.g. ICT, Parasight F, RAPIMAL) have been developed which allow the rapid self-diagnosis of

Table 2

Malarial standby treatment regimens

<i>Medication</i>	<i>Resistance</i>	<i>Adult dose</i>	<i>Reduce dose for children</i>
Atovaquone/proguanil	No	four tablets (250 mg/100 mg) daily for three days	< 40 kg
Mefloquine	Yes *	500 mg immediately, repeated eight hours later †	< 50 kg
Sulphadoxine-pyrimethamine	Yes	three tablets (500 mg/25 mg)	< 13 years
Quinine	No	600 mg three times daily for seven days ‡	< 50 kg

* Resistance has been reported in Thailand, Cambodia and Myanmar

† If < 60 kg use 250 mg for second dose

‡ Combined with sulphadoxine-pyrimethamine (in sensitive areas, three tablets) or doxycycline (100 mg twice daily for seven days)

malaria. They are immunochromatographic card tests that use a drop of blood to detect malarial antigens. These tests have been shown in numerous laboratory studies to be very sensitive and specific for falciparum malaria. As such they are well suited to long-term travellers who may not be taking prophylaxis, or who are taking a less effective prophylactic regimen, especially in those who are living without close access to medical care. They are easy to carry, simple to use, and give a quick result. However, studies have shown that many travellers have difficulty using them accurately in the field. These kits should therefore only be prescribed after appropriate instruction and training in their use.⁵

Summary

There is no ready solution to antimalarial prophylaxis for the long-term traveller or expatriate. Their doctor needs to be familiar with malarial epidemiology and drug resistance patterns in the area to be visited, the pros and cons of the various prophylaxis and treatment options, and the medical history and personality of the traveller involved. With this in mind, and with the provision of sufficient time for discussion with, and education of, the traveller, a suitable and safe regimen can usually be devised.

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FURTHER READING

See resources on the following web sites:

US Centers for Disease Control and Prevention www.cdc.gov/travel

World Health Organization www.who.int/ith/

Health Canada www.travelhealth.gc.ca

Department of Public Health and Travel Medicine, James Cook University
www.jcu.edu.au/school/phtm/PHTM/putravel.htm

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 75)

7. Doxycycline is unsuitable for malaria chemoprophylaxis in pregnant women.
8. Mefloquine should not be used for self-treatment by someone who has been taking it for malaria chemoprophylaxis.

Dental notes

Prepared by Associate Professor R.G. Woods and Associate Professor N. Savage of the Australian Dental Association

Managing dental patients receiving warfarin therapy

Warfarin is an anticoagulant which inhibits synthesis of the vitamin K-dependent coagulation factors II, VII, IX and X. Indications for anticoagulation are increasing, and dentists will be consulted by patients taking warfarin.

The activity of warfarin is expressed using the international normalised ratio (INR).¹ A normal coagulation profile has an INR of 1.0. The desirable INR range for patients depends on the condition being treated. Patients receiving treatment for deep vein thrombosis have a lower target range than those with prosthetic heart valves.² The risk of bleeding increases exponentially as the INR rises. Gingival bleeding can indicate a raised INR. Oral surgery can be completed safely with an INR from 1.5 to 2.5.³ A small study has suggested that with appropriate local measures to reduce bleeding, teeth may be removed by simple extraction with an INR of 2–4.⁴ However dentists should still be cautious before they remove teeth where the INR exceeds 3.

The possibility of postoperative bleeding in patients taking warfarin concerns dentists. However, before deciding if warfarin therapy should be interrupted the risk of perioperative or postoperative bleeding must be balanced against the risk of thromboembolism.²

Before dental treatment a thorough medical history should be obtained including details of any condition likely to be treated with warfarin. The dentist should also consider possible drug interactions with warfarin.⁵ Medications including antibiotics such as metronidazole, herbal remedies and alcohol may unpredictably alter the INR. If an interaction is considered likely or if the effect of any prescribed medication is not known, the dentist should consult the doctor supervising the patient's anticoagulant therapy. The INR should be checked before surgery.

For routine conservative dental treatment including scaling, changing an established warfarin regimen is not justified.⁶ In

most cases of dento-alveolar/oral surgery, including simple extraction of teeth, bleeding can be controlled in a reasonable time by minimising the extent of surgery to one site or quadrant, and using firm sutures or firm postoperative packs over the wound. Preferably surgery should be performed in the morning to facilitate postoperative observation. For extensive surgery the assistance of the physician supervising coagulation therapy is required to assist in determining whether a change of coagulation therapy is indicated.

Where the operative site is infected the use of antibiotics should be restricted to a preoperative prophylactic dose and postoperative antibiotics should be discontinued as soon as reasonable. Prolonged use of broad spectrum antibiotics should be avoided as it may change the effectiveness of warfarin by altering gut microflora compromising availability of vitamin K. Aspirin and non-steroidal anti-inflammatory drugs may also increase the risk of bleeding.

Local anaesthetics should be given cautiously avoiding venepuncture. To avoid the needles becoming barbed and tearing tissues, they should be used once only for each mucosal or skin puncture. Local vasoconstriction may be encouraged by infiltrating a small amount of local anaesthetic solution with 1:100 000 or 1:200 000 adrenaline close to the surgery site.

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