Malaria chemoprophylaxis: in war and peace

Despite recent and largely undeserved adverse publicity, mefloquine remains a useful antimalarial

Although malaria causes most suffering among children in the tropics, it should not be forgotten that it remains a major cause of military casualties. In September 2003, about 300 US Marines and support staff were deployed to Liberia, West Africa. Of those troops who spent at least one night ashore, 69 contracted falciparum malaria, an attack rate of 44%.[1] Forty-four required evacuation for medical care to Europe or the United States. While none died, several developed cerebral malaria and required mechanical ventilation. Malaria was also common among Australian Defence Force (ADF) personnel deployed to East Timor between 1999 and 2000, with 385 cases reported, an attack rate of 5%.[2] Eighty-four per cent of these cases were caused by *Plasmodium vivax*, which, while not life-threatening, causes significant morbidity. Relapse of *P. vivax* infection, caused by the re-emergence into the bloodstream of parasites lying dormant in the liver (so-called hypnozoites), was a major problem in this group, with 96 relapses reported despite 2 weeks of primaquine therapy.[2] This pattern of infection is frequently observed in patients who contract malaria elsewhere in Asia and the Pacific, as reported by Charles and colleagues in this issue of the Journal.[3]

Nevertheless, effective chemoprophylaxis is readily available for Australian travellers (Box). The challenge for medical practitioners is to select the most appropriate regimen and then to convince patients to use it.

Malaria chemoprophylaxis for areas with chloroquine-resistant malaria* (including the Pacific Islands, South-East Asia, the Indian subcontinent, China, Africa and South America)[4]

- Atovaquone + proguanil 250 mg + 100 mg (child > 40 kg and adult) 1 tablet orally, daily (starting 1 to 2 days before entering, and continuing until 7 days after leaving, malarious area)

OR

- Doxycycline (child > 8 years: 2 mg/kg up to) 100 mg orally, daily (starting 2 days before entering, and continuing until 4 weeks after leaving, malarious area)

OR

- Mefloquine (child 15 to 19 kg: ¼ tablet; 20 to 30 kg: ½ tablet; 31 to 40 kg: ¾ tablet) 250 mg orally, weekly (starting 2 to 3 weeks before entering, and continuing until 4 weeks after leaving, malarious area).

* Whatever chemoprophylaxis is prescribed, patients should be counselled that no prophylaxis is 100% effective, and the importance of mosquito avoidance should be emphasised.

Mefloquine as chemoprophylaxis

Much has been written (and broadcast) about the neuropsychiatric side effects of mefloquine. While a number of class actions have been instituted, none has as yet reached resolution. Identifying malaria chemoprophylaxis with any confidence as the cause of major psychiatric illness or behavioural disturbance is problematic,[5] even more so during or soon after exposure to an extremely stressful military environment. This issue is illustrated by allegations that mefloquine was responsible for fatal assaults committed by Canadian soldiers in Somalia and British soldiers in Sierra Leone, and that it contributed to the killings of spouses by US soldiers recently returned from Iraq. Similarly, it was alleged that psychiatric morbidity among ADF personnel who had been deployed to East Timor was attributable to mefloquine therapy.

While it is reassuring that in this issue of the Journal, Kitchener and colleagues report no excess morbidity among ADF personnel taking mefloquine prophylaxis,[6] the issue of tolerability of mefloquine is a real one. A double-blind, randomised controlled trial of malaria chemoprophylaxis comparing mefloquine and atovaquone–proguanil (Malarone [GlaxoSmithKline]) found that 139 of 483 (29%) participants taking mefloquine experienced an adverse neuropsychiatric side effect, most commonly insomnia or strange or vivid dreams.[7] Such side effects were reported in 69 of the 493 (14%) participants taking atovaquone–proguanil. The overall frequency of adverse events was similar in the two groups (71% and 67%, respectively), but the events were sufficiently severe to require discontinuation of the drug in 5% of those taking mefloquine versus 1.2% of those taking atovaquone–proguanil. Assessing tolerance to mefloquine before exposure (as undertaken by the ADF) might identify many of those intolerant of this drug, allowing an alternative agent to be selected.

Alternative agents for chemoprophylaxis

In Australia, doxycycline is the most widely prescribed drug for malaria chemoprophylaxis. While its side effects are relatively benign (eg, thrush, photosensitivity and oesophagitis), the challenge is to ensure compliance. Numerous studies have demonstrated that adherence to a daily prophylactic regimen is unsatisfactory, especially among those requiring long-term protection.[8] Atovaquone–proguanil is highly effective for chemoprophylaxis, but is costly and, like doxycycline, must be taken daily. There has been a resurgence of interest in primaquine as chemoprophylaxis, a drug generally used to prevent relapse of *P. vivax*. However, it too must be taken daily for prophylaxis and, like many other old "off-patent" orphan drugs, it is inordinately expensive. Tafenoquine, a much-anticipated drug related to primaquine, is now in phase III clinical trials. After three well-tolerated loading doses, a single monthly dose appears protective.[9] However, like primaquine, it can cause severe haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. Thus, it is necessary to screen for this condition before beginning the drug.

New agents for treating malaria

As Davis and colleagues discuss in this issue, artesunate is a highly effective and well tolerated antimalarial agent.[10] It belongs to the artemesinin class of drugs derived from the Chinese wormwood plant *qinghaosu*, and is taken by many expatriates as "emergency standby treatment" at the first sign of fever (unpublished observation). While this practice is effective, particularly when combined with appropriate diagnostic tests, such as the rapid antigen test used in the case reported in this issue by Howden and colleagues,[11] it is

not without risk. The very short half-life of the active metabolite, dihydroartemesinin, means that any parasites remaining in the blood after a short course of therapy may not be cleared, leading to recurrent parasitaemia.[10] Suitable drugs to combine with artesunate include mefloquine, doxycycline (if taken for one week), or, in the few regions where these drugs remain effective, combined pyrimethamine and sulfadoxine.[10] Further risks of relying on emergency standby treatment alone include failing to recognise non-classical symptoms of malaria (such as diarrhoea), and exhausting drug supplies through premature self-medication for non-malarial illnesses. Of note, counterfeit artesunate is offered for sale in several Asian countries where pharmaceuticals are unregulated; the only artemisinin derivative available in Australia is artemether in combination with lumefantrine.[10]

A malaria vaccine

An effective malaria vaccine suitable for non-immune soldiers, travellers and the even larger population of residents of malaria-endemic countries remains a priority. The long-standing search for a vaccine has been invigorated by the creation of the Malaria Vaccine Initiative, a public–private partnership supported by the Bill and Melinda Gates Foundation. The recently published phase II malaria vaccine trial in Mozambique involving this initiative and GlaxoSmithKline Biologicals is an example of the productivity of this partnership.[12] While the vaccine produced a statistically significant level of protection (29.9% to 57.7%), it is likely that, for now, doctors will continue to advise mosquito avoidance and to reach for the prescription pad rather than the vaccine refrigerator when preparing patients for trips to malarious areas.

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