Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor

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ABSTRACT

Objectives: To describe the tolerability of mefloquine in Australian soldiers for malaria prophylaxis, including a comparison with doxycycline.

Design: Open-label, prospective study and cross-sectional questionnaire and interview.

Setting and participants: Two contingents of Australian soldiers, each deployed to East Timor for peacekeeping duties over a 6-month period (April 2001–October 2001 and October 2001–May 2002).

Outcome measures: Withdrawals during the study; adverse events relating to mefloquine prophylaxis; willingness to use mefloquine again on deployment.

Results: Of 1157 soldiers starting on mefloquine, 75 (6.5%) withdrew because of adverse responses to the drug. There were three serious adverse events of a neuropsychiatric nature, possibly relating to mefloquine. Fifty-seven per cent of soldiers using mefloquine prophylaxis reported at least one adverse event, compared with 56% using doxycycline. The most commonly reported adverse effects of both drugs were sleep disturbance, headache, tiredness and nausea. Of the 968 soldiers still taking mefloquine at the end of their deployments, 94% indicated they would use mefloquine again. Of 388 soldiers taking doxycycline prophylaxis who were deployed with the first mefloquine study contingent, 89% indicated they would use doxycycline again.

Conclusions: Mefloquine was generally well tolerated by Australian soldiers and should continue to be used for those intolerant of doxycycline.

MJA 2005; 182: 168–171

A limited number of drugs are available for malaria protection, particularly for long-term prophylaxis. In 2001, doxycycline, mefloquine and Malarone (a combined preparation of atovaquone and proguanil) were recommended by the World Health Organization and the US Centers for Disease Control and Prevention for non-immune travellers in malarious areas where chloroquine-resistant *Plasmodium falciparum* malaria is prevalent.[1,2] Like travellers, military personnel must also take chemoprophylaxis in malarious areas, to minimise non-battle casualties.

In 1999, the Australian Defence Force (ADF) participated in an international peacekeeping operation in East Timor. During the first 5 months of the operation, 64 soldiers presented with malaria in-country.[3] Most soldiers had been prescribed daily doxycycline (100 mg) for prophylaxis, and these cases are believed to have resulted from poor compliance. These findings provided the stimulus to look at other chemoprophylactic options for soldiers in East Timor. During 2000–2001, a double-blind trial comparing weekly tafenoquine and mefloquine was conducted in Australian soldiers in East Timor.[4] Mefloquine was found to be well tolerated and accepted by the soldiers, and, as a result, there were requests for wider use of mefloquine from subsequent military units and soldiers being deployed to East Timor.

There are limited data on the tolerability of mefloquine for long-term prophylaxis in military personnel. Short-term studies (ranging from 2 to 5 months) in British, Dutch, Indonesian, Italian and US soldiers have shown weekly mefloquine to be safe and well tolerated.[5-9] To expand on our previous study in East Timor,[4] we monitored the tolerability of mefloquine in a larger number of Australian soldiers under peacekeeping conditions during two 6-month periods. We report here our preliminary findings.

METHODS

The study was carried out in two contingents of Australian soldiers, each deployed for 6 months on peacekeeping duties on the border between East Timor and Indonesia. The first contingent was deployed from April 2001 to October 2001 and the second from October 2001 to May 2002. Before enrolling, the soldiers received briefings in Australia regarding vector-borne diseases, personal protection measures, and information on the use of mefloquine and the nature of the study. Those choosing to enrol in the study signed an "information and consent" form. They were advised in the form and verbally that enrolment was voluntary and that they could withdraw from the trial at any time. Common, uncommon and rare side effects associated with mefloquine use (detailed in the manufacturer's product insert) were presented during enrolment and were listed in the information and consent form. Soldiers choosing not to enrol in the mefloquine study received doxycycline.

Soldiers meeting the inclusion criteria of fitness for deployment and providing informed consent were administered a loading dose of one 250 mg tablet of mefloquine (Lariam, Roche, Switzerland) given every other day on three occasions, followed by regular weekly doses of one 250 mg tablet.

After 6 months' deployment, the trial participants completed a health questionnaire followed by a structured interview, conducted by a clinical investigator, about adverse events. At the end of the first contingent's deployment, all soldiers being medically processed for return to Australia were invited to complete the health questionnaire

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— including soldiers who had withdrawn from the mefloquine study, those who had used mefloquine but were not participants in the study, and those who had used doxycycline only.

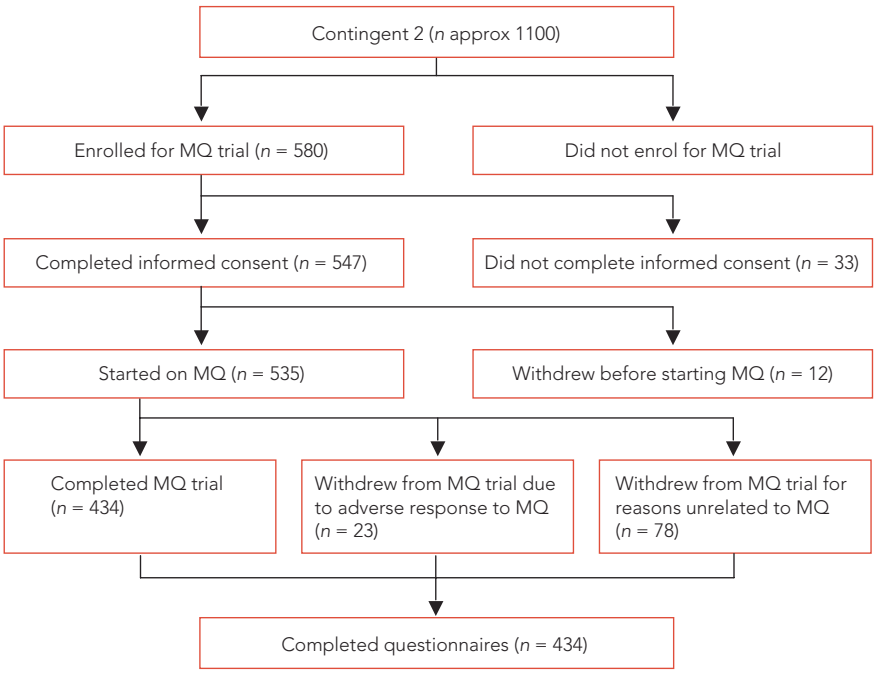
Participants were asked to grade the severity of any adverse events as (i) mild (not affecting daily activities), (ii) moderate (causing some interference with daily activities), or (iii) severe (preventing completion of daily duties). The adverse events were classified into body systems: gastrointestinal (including nausea, vomiting, diarrhoea and abdominal pain); constitutional (including headache, tiredness and malaise); neuropsychiatric (including sleep disturbance, anxiety, irritation, depression, hallucinations, confusion and balance problems); dermatological (including rash, skin disorders and dermatitis); and musculoskeletal (including muscle and joint pain). A "serious adverse event" was defined as "an untoward medical occurrence resulting in death, causing a threat to life, requiring or prolonging hospitalisation, or resulting in significant disability or incapacitation". The principal investigator, in consultation with the clinical investigators, assessed serious adverse responses on a four-point scale for causality ("not related", "unlikely", "possible" or "probable").

Our study was approved by the Australian Defence Human Research Ethics Committee.

RESULTS

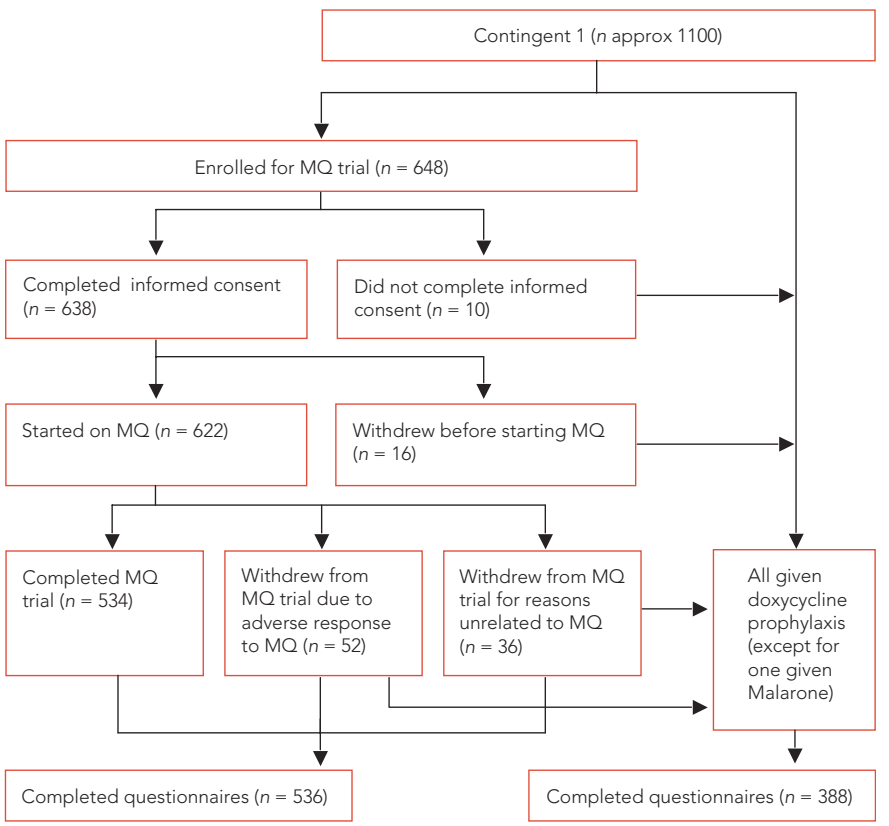
Of the 1228 soldiers who enrolled in the trial (648 in the first contingent and 580 in the second contingent), 1185 provided informed consent, of whom 1157 (1155 men, 2 women) started to take mefloquine (Box 1 and Box 2). Those who enrolled but did not start mefloquine prophylaxis either were not deployed for other reasons or chose not to continue after enrolment. Of the 1157 soldiers who started on mefloquine, 16.3% (189/1157) did not complete their deployment on mefloquine, and 6.5% (75/1157) had adverse responses to the drug. The withdrawal rate from mefloquine prophylaxis due to adverse effects of the drug was higher in the first contingent than in the second (8.4% v 4.3%). The body systems affected, as reported by soldiers who withdrew from mefloquine prophylaxis, are listed in Box 3. All soldiers who stopped taking mefloquine were given doxycycline instead (or Malarone, if they were doxycycline intolerant). Out of the first contingent, 388 soldiers were questioned about the tolerability of doxycycline prophylaxis during their deployment.

1 Participants in mefloquine trial in first contingent, Apr 2001–Oct 2001



MQ = mefloquine.

2 Participants in mefloquine trial in second contingent, Oct 2001–May 2002



MQ = mefloquine.

3 Adverse events, by body system, reported among Australian soldiers who withdrew from the mefloquine trial due to adverse effects of the drug*

Body system	First contingent withdrawals (*n* = 52)	Second contingent withdrawals (*n* = 23)
Gastrointestinal	6	4
Constitutional	9	9
Neuropsychiatric	42	20
Dermatological	3	3
Musculoskeletal	2	0

* Some participants reported more than one reason for withdrawing.

Serious adverse events

There were nine serious adverse events in the mefloquine arm of the study (four in the first contingent and five in the second), all occurring in men. Three of these men were withdrawn from the study because of neuropsychiatric symptoms possibly associated with mefloquine use. The first soldier had auditory hallucinations, which, on psychological assessment, were consistent with his undisclosed history of auditory hallucinations preceding mefloquine use and the episode in East Timor. The second soldier experienced heat illness while on patrol, with symptoms of nausea, dizziness and abdominal discomfort. He was observed to have a generalised seizure. However, he was later found to have an undisclosed history of epilepsy. He recovered with rehydration and was returned to Australia. The third soldier experienced depression, episodic anxiety, mild paranoia, short-term memory loss and suicidal ideation. Although he was taken off mefloquine and placed on doxycycline, his mental state continued to deteriorate. He was psychologically evaluated and returned to Australia.

Malaria incidence

During the trial period, only one soldier developed malaria while in East Timor. He had started on mefloquine but became infected with falciparum malaria after he had changed to doxycycline and had difficulty complying with the daily regimen.

Despite primaquine post-exposure prophylaxis, eight soldiers who were taking mefloquine presented with a primary episode of vivax malaria after returning to Australia.

Responses to health questionnaire

At the conclusion of the first contingent's deployment, 924 soldiers received health questionnaires, including 536 who had taken mefloquine chemoprophylaxis and 388 who had taken doxycycline. Of this group, 57% of soldiers reported one or more adverse events during their use of mefloquine compared with 56% of soldiers using doxycycline. Sleep disturbance, headache, tiredness and nausea were the most commonly reported adverse events (Box 4). A detailed report of adverse events, including data on the second contingent, will be published elsewhere.

Of the 968 soldiers still taking mefloquine at the end of their 6-month deployment, 96% and 92% from the first and second contingents, respectively, indicated that they would take mefloquine on their next deployment to a malarious area. Of the 388 soldiers in the first contingent who were questioned after using doxycycline, 89% indicated they would use it again on deployment.

DISCUSSION

In our study, the most common adverse events relating to malaria prophylaxis with either drug were sleep disturbance, headache, tiredness and nausea. Apart from mild sleep disturbance, which was more common in soldiers taking mefloquine, and mild tiredness, which was more commonly associated with doxycycline, the incidence of these adverse events was similar for both drugs.

Among the 1157 Australian soldiers taking mefloquine in our study, the 6.5% withdrawal rate from the drug due to adverse events was higher than among Italian soldiers on peacekeeping duties in Africa (0.9% of 1386),[8] British soldiers exercising in Kenya (3.4% of 183)[5] and US Marines stationed in Hawaii, USA (4.9% of 202).[9] The emotional and environmental pressures of peacekeeping operations in East Timor may have contributed to the higher withdrawal rate in the Australian soldiers compared with other military experiences with mefloquine.

In previous studies of mefloquine in military volunteers, no serious neuropsychiatric reactions were observed.[5-9] We observed three serious adverse events of this nature that were possibly associated with mefloquine use. This is a higher incidence than the 1 in 6000 to 1 in 10 600 reported in travellers.[1] However, two of the three soldiers involved had undisclosed pre-existing conditions that are contraindications for mefloquine use.

When monitoring the tolerability of a drug under military operational conditions, there is a need to account for the physiological and psychological stress associated with such activities that may confound the relationship between drug intake and adverse events. Thus, the tolerability of antimalarial drugs as assessed in these Australian soldiers may not be directly comparable to circumstances of recreational travel. Nevertheless, the withdrawal rate from mefloquine in our study was comparable to that reported in civilian travellers (range, 5%–6.5%).[10,11]

Furthermore, the cohorts in our study were not randomly allocated and therefore comparisons made may be biased. Our results are also subject to the limitations of self-report and memory.

4 Adverse events reported by Australian soldiers in the first contingent* after taking mefloquine (*n* = 536) or doxycycline (*n* = 388) for malaria prophylaxis in East Timor, Apr–Oct 2001

	Mild degree		Moderate degree		Severe degree	
	Mefloquine	Doxycycline	Mefloquine	Doxycycline	Mefloquine	Doxycycline
Sleep disturbance	128 (24%)	53 (14%)	33 (6%)	28 (7%)	2 (< 1%)	2 (< 1%)
Headache	53 (10%)	51 (13%)	17 (3%)	14 (4%)	1 (< 1%)	4 (1%)
Tiredness	72 (13%)	78 (20%)	20 (4%)	16 (4%)	0	1 (< 1%)
Nausea	86 (16%)	63 (16%)	22 (4%)	20 (5%)	4 (1%)	0

* Some participants reported more than one adverse event.

Despite the possibility of side effects associated with mefloquine (and other antimalarial drugs), this drug protects against potentially life-threatening infections that may also jeopardise the success of military operations. Malaria is endemic in East Timor, and, at the time of the first contingent's deployment, the prevalence of malaria among East Timorese in the area of deployment was as high as 35%.[12] The fact that a soldier not complying with doxycycline use developed malaria in East Timor, as did a small proportion of soldiers after returning to Australia, suggests that the participants were exposed to malaria infections in East Timor and that mefloquine was effective as a suppressive agent against blood stages of both falciparum and vivax malaria.

In conclusion, our study has been one of the largest tolerability trials of mefloquine and doxycycline conducted in military personnel. While the comparison must be interpreted cautiously in light of possible selection bias, it may be concluded that these drugs were generally well tolerated. As Australian soldiers will continue to exercise in and be deployed to malaria-endemic areas, there is a continuing need to seek out effective and well tolerated antimalarial drugs and to maintain alternative chemoprophylactic options. Enhanced surveillance of alternative antimalarial drugs under operational conditions will ensure that the most appropriate chemoprophylaxis is available for the ADF.

ACKNOWLEDGEMENTS

The authors would like to thank Private Michael Reid, Lieutenant Kieran McCarthy, Captain Anne Jensen, Captain Leith Baird, Captain Tracey Carthew, Captain John Cunningham, Captain Damien Woods, Squadron Leader Karen Leshinskas, Major Brett Robertson and Lieutenant Colonel Bob Cooper for either their medical or technical support towards the study. The opinions expressed are those of the authors and do not necessarily reflect those of the Defence Health Service or any extant ADF policy. The study was wholly conducted using the resources and personnel of the ADF.

COMPETING INTERESTS

The authors were full-time employees of the Australian Army Malaria Institute at the time this research was carried out and have no other conflict of interest to declare. The Australian Defence Human Research Ethics Committee, in accordance with National Health and Medical Research Council guidelines, requires all clinical research to be submitted for peer review.

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(Received 10 Nov 2004, accepted 21 Dec 2004) ❑