Evaluation of Safety and Adverse Effects of Mefloquine in the Chemoprophylaxis of Malaria In Non-Immune Australian Soldiers

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Table of Contents

List of figures:

List of tables:

Abstract

Background

Following the outbreak of malaria among Australian troops in East Timor during the International peacekeeping operations in 1999, an investigation was conducted which among other findings illustrated that the daily routine of doxycycline chemoprophylaxis was not well accepted and may be contributing to the infection rate.

Methods

The Fourth Battalion, Royal Australian Regiment, and attachment deployed to East Timor between April and October 2001. Mefloquine 250mg weekly was used for malaria chemoprophylaxis by 620 soldiers under the auspices of a study by the Army Malaria Institute.

Results

One soldier suffered malaria during the deployment while using doxycycline after ceasing mefloquine several months earlier. Overall, 93 soldiers changed to doxycycline, of which 74 were considered adverse responses to mefloquine. Sleep disturbances were the most commonly reported cause for withdrawal (24/74), mood disturbances (13/74) and no particular reason (12/74). At the conclusion of the deployment, 571 soldiers using mefloquine and 384 soldiers using doxycycline were questioned for adverse events. Only sleep disturbance was more common among those taking mefloquine (OR = 1.5; CI: 1.07-2.08; p = 0.01), while headache (OR = 0.61, CI: 0.41-0.92, p=0.01) and tiredness (OR=0.62; CI:0.44-0.89; p=0.006) were more common among those using doxycycline.

Conclusions

Mefloquine was a well-accepted and predictable malaria chemoprophylaxis for Australian soldiers in difficult conditions peacekeeping in East Timor. Nevertheless, mefloquine malaria chemoprophylaxis does not suit all soldiers under field conditions and the incidence of withdrawal from weekly mefloquine chemoprophylaxis was higher among ADF personnel than previously reported among civilian and military groups perhaps due to the stress of this operation or the nature of this study.

Adverse responses to mefloquine were generally present immediately following the loading dose. Sleep disturbance was a relatively more common adverse effect with mefloquine chemoprophylaxis (OR 1.5, p=0.01), apparently unrelated to the blood concentrations of mefloquine and typically resolving with perseverance.

No other adverse effects were more commonly associated with mefloquine chemoprophylaxis than that with doxycycline. Gastrointestinal effects, balance disruption and other mild neuropsychiatric events were comparable between mefloquine and doxycycline chemoprophylaxis.

Further research into the predictable characteristics of soldiers likely to respond badly to mefloquine chemoprophylaxis would be worthwhile for tailored use of mefloquine under operational conditions. Clearly, the pre-existence of sleep disorders, seizures, psychoses or other neuropsychiatric events contraindicate the use of mefloquine chemoprophylaxis.

Acknowledgments

I must acknowledge the soldiers of InterFET who were overwhelmed by malaria. One soldier particularly provided the motivation for this work. He had become a malaria casualty when I met him to provide some assistance. On history, he reported poor compliance with doxycycline chemoprophylaxis. He had missed doxycycline every three days as he found he could not eat while on the regimen. However, to keep up with his mates and not let the section down, he would take a third daily break - to eat. I am sure this is the Australian soldier, most Australians would want protecting their homeland. He deserves better than to be given a standardised malaria chemoprophylaxis regimen and sent out into a malarious storm. I saw him again 18 months later, as he prepared to go back to his duties in East Timor. He was well and thanked us for an alternative chemoprophylaxis, which he would try. He has not developed malaria yet.

I appreciate the love and support my family has provided and the sacrifices they have made for this period of my life. My apologies to them for not hearing my younger daughter's first sentence, "Daddy's in Timor"; leaving my wife with a newborn son and missing my elder daughter's first month at school. I cannot thank my wife enough for the understanding she has of my work and myself.

I would like to thank the staff of the Army Malaria Institute, particularly Captain Anne Jensen, Lieutenant Michael Reid, Captain Leith Baird and Lieutenant Colonel Peter Nasveld. I am particularly grateful to my Commanding Officer, Lieutenant Colonel Mike Edstein from whom I have gained a valuable apprenticeship and to Dr. Lindsay Brown for his advice and direction.

Pete Nasveld deploying forward to investigate a malaria outbreak in Australian InterFET troops, 1999.

With thanks to the Mefloquine trial team: (from the left of the author) Sergeant "Johno" Johnson, Lieutenant Michael Reid, Private Fran Bauman, Captain Larry Sargeant , Captain Ann Jensen (Study Coordinator), Captain Leith Baird, Lieutenant Kieran McCarthy, Warrant Officer Swann. Photographed at Port Herra, East Timor, October 2001.

Publications

The following are publications that have been accepted, related to this research.

Kitchener SJ, Nasveld PE, Russell B, Elmes N. An outbreak of malaria in a forward battalion in East Timor. *Mil Med.* In press.

attached at Annex A

Kitchener SJ, Warwarek P. Operational Malaria in East Timor: six battalions later. *Aust Mil Med*. In press.

- attached at Annex B

Kitchener SJ, Ashford B. Self treated relapsing vivax malaria? *Aust Mil Med*. In press.

- attached at Annex C

List of Abbreviations

ADF	Australian Defence Force
ADHREC	Australian Defence Health Research Ethics Committee
ADMEC	Australian Defence Medical Ethics Committee (predecessor to ADHREC)
ADR	Adverse Drug Reaction
AE	Adverse experience / event
AMI	Army Malaria Institute
AO	Area of operation
AR	Absolute Risk
AS	Australia
AUSBATT	Australian Battalion Area
AFRIMS	Armed Forces Research Institute of Medical Research
BDE	Brigade
CDC	Centers (US spelling) for Disease Control and Prevention
Cdo	Commando
CE	Clinical epidemiologist
CI	Confidence interval
CRF	Case Record Form
CSSB	Combat Service Support Battalion
CSST	Combat Service Support Team
CVD103	A strain of *S. typhi* modified for vaccine use at the Center for Vaccine Development (Baltimore)
DHSB	Defence Health Service Branch
DX	Doxycycline

ELISA	Enzyme linked immunosorbent assay
EM/ET	East Timor
HPD	Health Policy Directive
HPLC	Human Plasma Liquid Chromatography
ICT	Immunochromatographic Test
InterFET	International Force in East Timor
LHQ	Land Headquarters
MSP	Mefloquine with sulfadoxine and pyrimethamine
MQ	Mefloquine
OR	Odds Ratio
PCV	Packed Cell Volume
PM	Preventative Medicine
RAR	Royal Australian Regiment
RTA	Return to Australia
SAE	Serious Adverse Event
SD	Standard deviation
SO	Staff Officer
SST	Serum Sample Tube
Ty21a	*S. typhi* strain modified for vaccine and vector use
UN	United Nations
UNTAET	United Nations Transitional Administration in East Timor
WHO	World Health Organisation
WR142490	The reference number allocated to mefloquine
WRAIR	Walter Reed Army Institute of Research

Chapter 1 - Introduction

East Timor

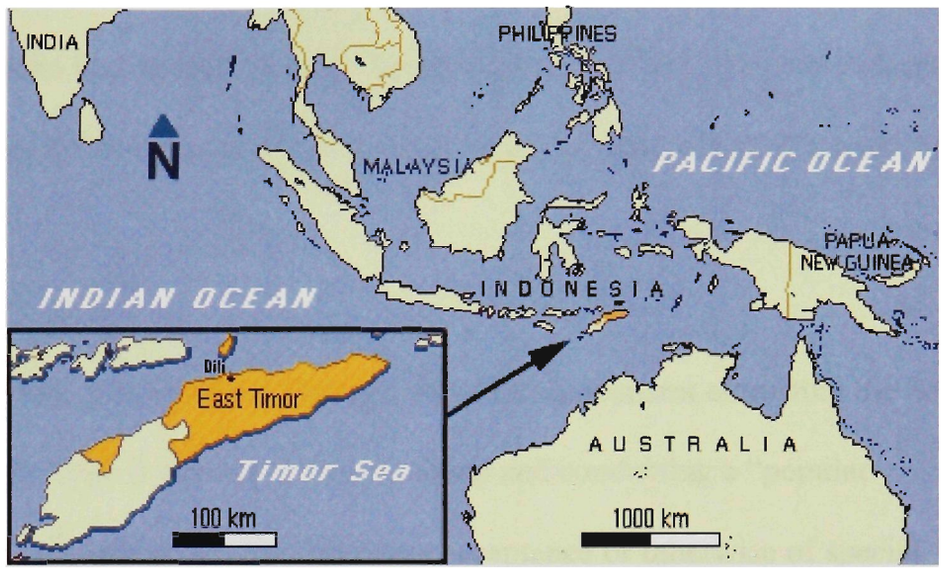


Figure 1: East Timor in Australasia

In 1949, the Netherlands transferred sovereignty of that nation's interests in South East Asia to the Republic of Indonesia. Australia had taken a major role in referring the conflict in Indonesia following the Second World War to the United Nations as a breach of Article 39. This was quite a revolutionary stance at the time, which recognised that security in the area depended upon mutual co-operation and respect of all Asian nations[1].

In 1960, the United Nations General Assembly added East Timor to the list of recognised Non-Self-Governing Territories, as Portugal had administered the area for nearly 500 years. In 1974, following an attempt to establish self-government, civil war broke out between those favouring the move and those in support of integration with Indonesia. Portugal withdrew and Indonesia integrated East Timor as a province in a military action. The United Nations called for withdrawal[2].

On 27 January 1999, Xanana Gusmao, a leading figure in the East Timor pro-independence movement, was released from prison in Jakarta with the announcement by President Habibie that Indonesia would consider independence for the Province. While Australia had an interest in a smooth transition of East Timor to independence, it was considered that a peacekeeping force would be unnecessary (Downer, March 1999).

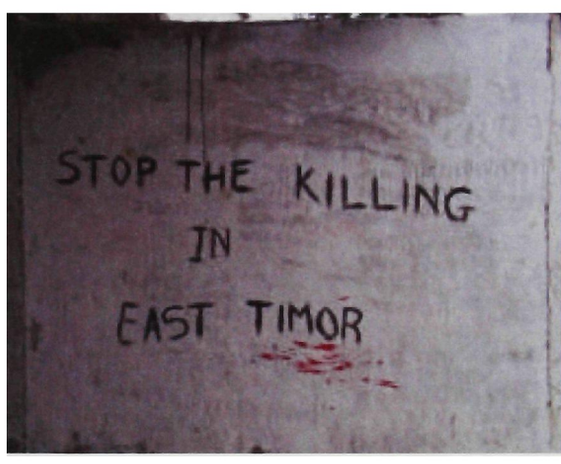
On 5 May 1999, Indonesia and Portugal signed an agreement entrusting the Secretary General of the United Nations with organising and conducting a "popular consultation" regarding the East Timorese acceptance or otherwise of special autonomy from Indonesia. The United Nations established a mission for this function[3,4] On 30 August 1999, the people of East Timor voted overwhelmingly for independence from Indonesia. However, civil unrest prior to and following the referendum prompted deployment of a multinational peacekeeping force authorised by the United Nations Security Council Resolution 1264. On 21 September 1999, the Australian Prime Minister moved that the House of Representatives endorse agreement with the United Nations Secretary General's request that Australia contribute to and lead the force[5] – the International Force in East Timor (InterFET). Interestingly, that morning, 1500 troops had already landed in East Timor.

At this time in history, East Timor had a population of almost 900 000, an infant mortality conservatively estimated at 70/1000 and over 10000 cases of malaria confirmed per annum[6] Detailed WHO investigations in 1998 demonstrated a blood slide positive rate of 49%. The report concluded "increased malaria transmission with increased morbidity and mortality can be expected within the next few weeks."

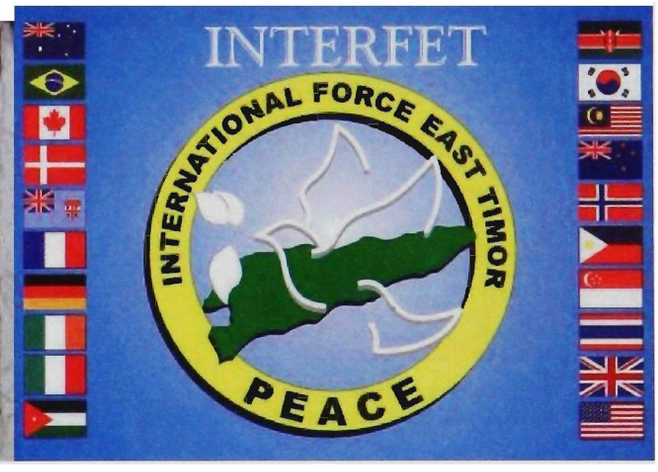
Earlier observations of malaria in Timor had shown a high parasitaemia rate in village dwellers with *Plasmodium falciparum*, *P. vivax* and *P. ovale*[7]. At this time (1975), no resistance was identified, however, 62.8% of hospital cases treated in 1990 demonstrated chloroquine resistance[8]. Levels of resistance were considered low in East Timor compared to other areas of Indonesia and was identified as particularly low to mefloquine (4.8%) on in vitro testing9.

In September 1999, the World Health Organisation recommended mefloquine or doxycycline prophylaxis against malaria[6].

The Australian Defence Force involvement



Dili, East Timor, 1999



International Force in East Timor

Also in September 1999, the Australian Defence Force (ADF) led the InterFET to re-establish peace after civil unrest had overtaken the Indonesia Province in the wake of a referendum overwhelmingly endorsing independence.

The Australian elements of InterFET included three Battalions, which moved forward from Dili to patrol the northern border region of East Timor. The Second Battalion, Royal Australian Regiment (RAR) secured Headquarters in Balibo, the Third Battalion, RAR, based in Maliana and the Brigade Headquarters was established in Suai with Australian, New Zealand, Canadian and Irish elements.

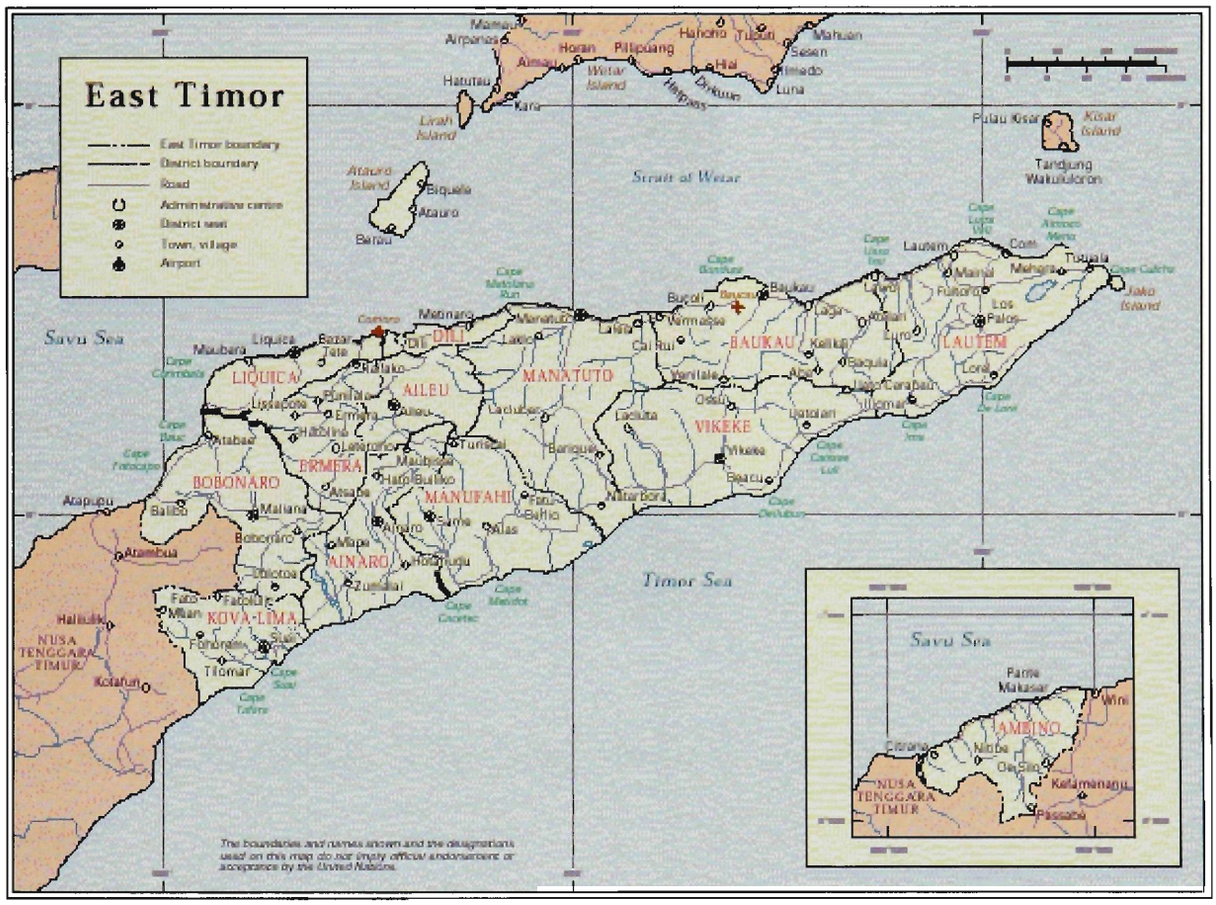


Figure 2: Map of East Timor

East Timor is part of a mountainous island. The central highlands fall away gradually on the southern shores to wetlands and more precipitously to seasonally arid country on the north aspect. The Second Battalion, RAR, based Company strength elements forward to the border regions west of Balibo.

In early October, 1999, C Company headquarters was in Batugade near the border with West Timor on the north coast of the island. The Company position was in and around an old Portuguese fort on the beach of the Savu Sea. This period was punctuated by an exchange of gunfire between Indonesian TNI Forces and ADF troops (C Company) on 10 October 1999 forward of Batugade at Motaain when a dispute arose regarding the position of the border. Elements of the Support Company from Balibo were dispatched to secure the area overnight.

Piquet duty, Batugade 1999

(NB. Captain Bruce Russell identifying Anopheles mosquitoes, centre left of picture)

On 23 October 1999, the first of 73 cases of malaria presented from the Australian contingent (approximately 5500 persons) of InterFET, from Support Company, Second Battalion, RAR, based in Balibo. In the following few days, six more cases of malaria presented in Balibo, mostly from C Company.

Deploying, Komoro airfield, Dili, 1999

Captain Bruce Russell and I deployed from Army Malaria Institute (AMI) for initial descriptive, epidemiological and entomological investigations of this outbreak.

Malaria cases continued to present among the Australian InterFET troops. The Third Battalion, RAR, based in the Enclave of East Timor began receiving casualties shortly after my arrival.

Naktuka, the Enclave of East Timor, 1999

Investigation of the initial three cases suggested the infection was contracted during a single evening spent in a high transmission location during a patrol through Naktuka, near the far western border of the Enclave.

These cases were medically evacuated by air under difficult circumstances, due to the isolation of the Enclave.

Arrival for dust-off of casualty

The case control conducted study found that there were several systemic factors contributing to the outbreak with intolerance of doxycycline as a major risk factor for contracting malaria[10] The ultimate impact of malaria on ADF troops who served in the InterFET operation has been significant with 389 episodes of malaria attributed during and after the operation[11]

Balibo Fort, 1999

My continued engagement with Australian Defence operations in East Timor has all arisen from this investigation. This study of the operational suitability of mefloquine is in direct response to the findings implicating doxycycline failure in the initial outbreak of malaria among Australian soldiers on the border of East and West Timor.

The AMI subsequently deployed to East Timor again in February 2000 at the conclusion of the InterFET Operation in an attempt to mitigate the impending outbreak of vivax malaria. The initial outbreak, while predominantly involving *P falciparum* infections indicated many Australians had been exposed to malaria and many would manifest *P. vivax* infections when chemosuppression with doxycycline

ceased. Primaquine terminal prophylaxis had been prescribed, however, as AMI had undertaken trials with another 8-aminoquinoline, tafenoquine, in Bougainville, it was considered that this may more efficiently reduce subsequent vivax malaria incidence. My role was the trial clinician on the team led by Lieutenant Colonel Mike Edstein.

The first Battalion to serve following InterFET was the Sixth Battalion, RAR, from April 2000. This Battalion Group used doxycycline chemoprophylaxis and sustained seven malaria casualties during deployment. Following this, the First Battalion, RAR deployed using weekly chemoprophylaxis with either tafenoquine or mefloquine in a blinded clinical trial. No malaria cases were recorded during this deployment. It was the impetus of acceptance of weekly chemoprophylaxis and apparent success of mefloquine (prior to unblinding) that supported further investigation of mefloquine weekly chemoprophylaxis in the open label trial with the Fourth Battalion, RAR.

Background on Malaria

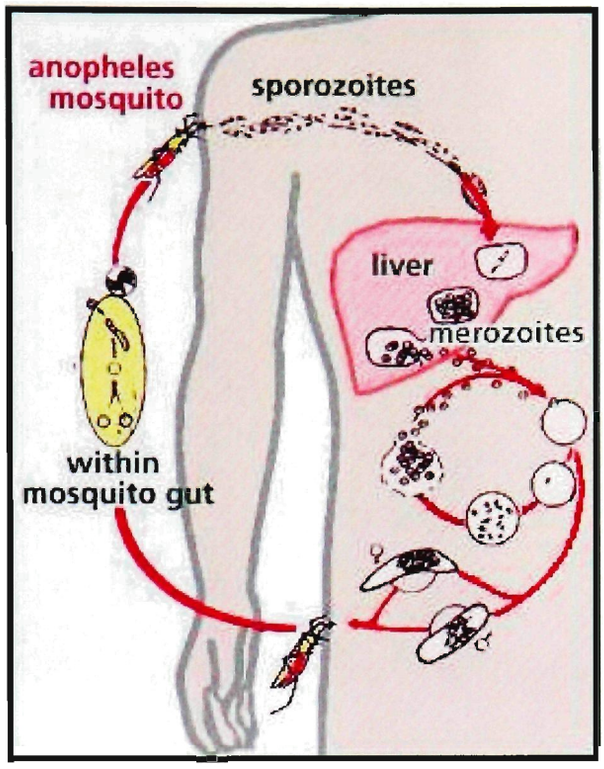


Figure 3: Life cycle of the malaria parasite

Familiarity with the life cycle of malaria parasites is necessary to understand the efficacy of antimalarial agents. Parasitic protozoa of the genus *Plasmodium* cause malaria. Four species infect humans and insects alternatively. These species are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*.

Surgeon Major Ronald Ross on 20 August 1897 determined that mosquitoes of the genus Anopheles transmit the parasites to humans via blood meals. The sexual stage of the parasite life cycle involves multiplication from gametocytes acquired in a previous blood meal. This occurs in the stomach wall before migration to the salivary glands from which infection of humans occurs during a subsequent blood meal[12].

Major Ronald Ross

Mefloquine acts on the blood stages of the life cycle, after the release of merozoites from the liver, in all four species of malaria infecting humans[13] It does not have tissue schizonticidal activity, specifically against liver stages, therefore, does not "cure" those forms of malaria retaining late liver stages, hypnozoites, as occurs in the life cycle of *P vivax* and *P. ovale*[14] Similiarly, it does not act against the sexual stages taken up by the mosquito in the life cycle, therefore does not block transmission.

The recommended regimen for malaria prophylaxis with mefloquine is 250mg weekly beginning with three doses prior to exposure. While established treatment for malaria in non-immune individuals is 25mg/kg, or 15mg/kg for semi-immune individuals given as a single dose[15], the ADF follows a split dose regimen of 15mg/kg to reduce adverse effects[16]

Chapter 2 – Literature Review

The development of mefloquine as an antimalarial agent

The bark of the cinchona tree chewed or made into an infusion was probably long known by people of the Inca tribes to treat febrile illnesses before it first attracted European attention. In 1630, a Jesuit, Juan Lopez is reputed to have provided an infusion of a powdered tree bark to the wife of the Viceroy of Peru, Countess Cinchon for the treatment of an ague. On recovery, the Countess in her beneficence provided the powder to the poor of Peru for treatment of illness. The bark was exported to Spain from 1641. At this time, the Iberian Peninsula and southern Europe were endemic for malaria and the new treatment was steadily accepted for the treatment of ague[17]

Juan Lopez administering treatment to the Countess Chincon (source unknown)

James Lind in 1765 described the specific use of the powdered bark in an attempt to reduce the indiscrimant use which had developed following listing in the London Pharmacopeia by 1677 Linnaeus named the tree that produced the bark, Cinchona, after the Countess Cinchon, in 1749. In 1820, Pelletier and Caventou isolated the alkaloids quinine and cinchonine. This allowed accurate dose prescribing and assay of alkaloid content in bark lots[18]

The next milestone in the development of antimalarials was in 1865 when seeds were extracted from a crop of trees in the Bolivian Andes and smuggled out to London. The Dutch Consul purchased these for plantations in Java[19] This diversified the production of cinchona alkaloids, though did not alter the course of antimalarial development greatly other than perhaps making cinchona more available. However within fifty years these plantations produced most of the world's supply of cinchona alkaloids available[20]

In 1926, the 8-aminoquinolines, pamaquine and later primaquine were the first synthetic antimalarials produced by German pharmaceutical companies. Following these compounds were the 4-aminoquinolines, which led to sontoquine and chloroquine in the inter-war years[21]

In December 1941, Japan invaded Malaysia and through Singapore to the Indonesian archipelago gained control of the oil fields of the area to fuel their expanding empire. Collateral acquisitions in this action were most of the cinchona plantations supplying quinine to the rest of the world, including Allied Forces[22] Severe restrictions in supply of quinine developed following the occupation of Java and the majority of

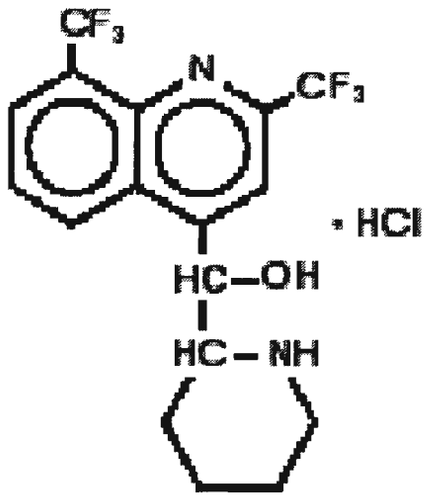
cinchona trees coming under Japanese control. Non-battle casualties among Australian and British Forces in New Guinea and Burma were becoming crippling. The Australian Army Land Command responded by raising the Medical Research Unit (1MRU) under Hamilton Fairley[23].

1MRU: Brigadier Hamilton Fairley (right)

The MRU was particularly successful in developing atebrin (mepacrine) for operational use in the New Guinea Campaigns. This Unit was the forerunner to the present Army Malaria Institute.

As has become a recurring theme in the development of antimalarials, these military events and the potential for increasing non-battle casualties stimulated research and development of antimalarials. Wellcome Pharmaceuticals re-discovered data held on sontoquine and chloroquine[17] In the United States, the Walter Reed Army Institute of research (WRAIR) increased research into chloroquine following the success of mepacrine (atebrin)[24], as well as continuing further research into means of prolonging the antimalarial effects of cinchona alkaloids[25]

The research and development of synthetic antimalarial drugs had been accelerated. Following the 1939-45 war, several allied nations became involved in land wars in South East Asia and again began sustaining non-battle casualties from malaria. At this time, it was noted that cinchonine and quinine both were apparently metabolised by oxidation at the 2-position of the cinchona side chain. Substitution at this position led to compounds with greater activity in avian malaria[26]



WR 142490, Mefloquine

Quinonlinemethanols such as mefloquine were developed based on observation of the metabolism of quinine and other cinchona alkaloids. A potential opportunity to increase the antimalarial activity of the compounds existed by delaying the metabolism to inactive substrates. Approximately 120 compounds were produced at

WRAIR in this line of research. The lead compound from this direction was WR30090 representing the class 2-phenyl-4-quinonlinemethanol, the second generation of quinonlinemethanols from quinine and the cinchona alkaloids[26]

All arylaminoalcohol antimalarials developed by WRAIR were blood schizonticides, which were useful in suppressive chemoprophylaxis and in radical cure of non-relapsing malaria. Without adequate penetration to tissue phases of relapsing malaria, these compounds do not provide true causal prophylaxis against all species of malaria. For the purposes of managing the more severe species of *P. falciparum*, blood schizontical agents were adequate in suppressive chemoprophylaxis, clinical disease mitigation, and cure, when resistance had not developed[21]

The Walter Reed Army Institute of Research produced WR30090 directly after the end of the 1939-45 War arising from the increased efforts to find replacements for quinine. Notably, development was slow, with some animal model testing and toxicology in the following 20 years. Preclinical trials of WR30090 began to appear in the literature more frequently after this time. Much of the research into blood schizonticidal agents to replace quinine and particularly chloroquine was driven by the development of *P. falciparum* resistant to chloroquine. The escalation of preclinical trials with WR30090 coincides with the appearance and escalation of chloroquine-resistant falciparum malaria particularly in locations of military interest to the United States in South East Asia and South America[22]

Notwithstanding the extensive biochemical and toxicological studies performed on WR30090, when research did accelerate, the potential of the class began to appear

with subsequent animal studies. The commonly used animal model for *P. falciparum* infections in humans is that of *P berghei* in mice. WR30090 approached complete effectiveness against *P berghei* strains sensitive and moderately resistant to chloroquine. In the mouse model, however, it failed against *P berghei* highly resistant to chloroquine[27] It was also found to be effective against *P. cynomolgi* in rhesus monkeys, a model for relapsing malaria[28] Unfortunately, WR30090 did not produce the high cure rates previously observed against *P falciparum* strains resistant to chloroquine, or pyrimethamine or both, in Aotus monkeys[29]

In early clinical trials[30], WR30090 was well tolerated and completely cleared blood schizonts of *P falciparum* including strains moderately and highly resistant to chloroquine. Against *P. vivax*, 84% (6/7) of trophozoite-induced infections were cleared, while sporozoite infections were predictably not cured (as mefloquine does not affect tissue phases which cause relapsing vivax malaria). It was also effective and well tolerated as a chemosuppressive prophylactic agent in non-immune humans infected with chloroquine and pyrimethamine-resistant *P falciparum,* and the New Guinea Chesson and Vietnam strain of *P vivax*[31]

Resistant falciparum malaria has spread rapidly to most malarious areas of the tropics. The imperative to produce antimalarial agents was to meet this growing challenge. Therefore, WR30090 was taken to Thailand for treatment trials directly against known chloroquine-resistant falciparum malaria. WR30090 performed well including in early phase clinical trials against chloroquine-resistant *P. falciparum* infections in Thailand. However, this drug produced a series of neurological and gastrointestinal adverse events and was cumbersome to use in the field[32]

With the limitations of WR30090, WRAIR developed WR142490 by the substitution of the 2-phenyl group by a trifluoromethyl group. The new compound was designated "mefloquine" and heralded as a solution to developing resistance in *P. falciparum*[33]

The efficacy of mefloquine as a prophylactic agent against falciparum malaria[34] was published in 1974, and for treatment of malaria in 1975[35] The suppressive activity of mefloquine against sporozoite induced infection in human volunteers was reported by Clyde and colleagues in 1976[36]

The development of mefloquine was timely, though not unrelated to the appearance of malaria resistant to available pharmaceutical agents. Mefloquine was quickly determined to be effective against known resistant strains of *P. falciparum* including those isolated in the South East Asian region[37] It became installed as the standard for management of such cases[38] For the ten years after these initial pre-registration trials, Phase II and III field trials continued to demonstrate the effectiveness of mefloquine in areas of known chloroquine-resistant falciparum malaria in Africa[39], South-East Asia[40,41], China[42] and South America[43,44,45] including for children with complicated malaria[46] Some trials also indicated equivalent efficacy with chloroquine in treating vivax malaria[47]

Clinical evidence of parasites resistant to mefloquine began to appear in the Australasian region approximately at the time of general availability[48] With increasing resistance in Africa and India, strategies to "protect" new agents such as mefloquine were suggested[49] in an attempt to slow the development of resistance.

One strategy to delay development of resistance to antimalarial drugs is to use combinations of mefloquine with sulfadoxine and pyrimethamine (MSP). Initial use of MSP did not produce apparent benefits[48], though the combination did become a preferred therapeutic option in areas of known or suspected mefloquine resistance in Asia[50] and Africa[51]

Adverse events associated with mefloquine treatment for malaria

The adverse effects of mefloquine have been largely determined from studies of patients being treated for malaria with mefloquine rather than those using mefloquine for suppression of malaria during transient exposures in endemic or epidemic areas. Early reports of pathophysiological effects of mefloquine recognised respiratory and particularly cardiovascular influences[52], though mefloquine was being used in conjunction with quinine for treatment of complicated falciparum malaria[53]

In South East Asia in the 1980's, mefloquine was well tolerated in field trials for the treatment of vivax[54], malariae[55] and falciparum malaria compared to Fansidar (500mg sulfadoxine and 25mg pyrimethamine)[56] Mefloquine was well tolerated and the combination highly effective in combination with sulfadoxine and pyrimethamine (MSP)[51,57] was highly effective against falciparum malaria and well tolerated by the recipients. Some treatment studies demonstrated a cluster of gastrointestinal and neuropsychiatric adverse responses following therapeutic bolus doses of mefloquine for acute falciparum malaria[58]

Descriptions of major adverse responses to mefloquine became available after broader availability of the drug for treatment in 1986. Phase III trials notably began to report

less favourable adverse response profiles in treatment with mefloquine and MSP, than initial reports. Blinded comparison of mefloquine to MSP treatment of Thai patients did not demonstrate any difference in adverse events during treatment of acute falciparum malaria. However, gastrointestinal side effects were significantly more common in those patients of either group who had not experienced these symptoms prior to onset of treatment[59] In Vietnam, a competitive trial of mefloquine and MSP for the treatment of acute falciparum malaria also demonstrated gastrointestinal side effects, especially vomiting which caused four of the 120 participants to be changed to alternative treatment[60] The gastrointestinal effect may be related to a racial predisposition or age as Nigerian children with uncomplicated acute malaria, tolerated MSP, mefloquine and chloroquine equally well[61]

With the increase in chloroquine-resistant falciparum malaria in South East Asia, other combinations were trialed including mefloquine or MSP with tetracycline. Tetracycline 250mg four times daily for seven days with 1000mg mefloquine was compared to the same tetracycline dose with four tablets MSP (each 250 mg mefloquine, 500 mg sulfadoxine and 25 mg pyrimethamine)[62] No difference was found between adverse events during the acute stage of treatment, though the randomised trial only had 50 patients. A reasonably high recrudescent rate (6/50) was linked to adverse events as two of these cases had sustained vomiting which was thought to be associated with treatment and the potentially of lowering drug absorption.

In the early 1990's, higher dose mefloquine was been used in areas of South East Asia against multi-drug resistant falciparum malaria, including mefloquine-resistant strains.

A mefloquine dose of 25mg/kg compared to standard 15mg/kg in the treatment of multi-drug resistant falciparum malaria on the Thai-Myanmar border identified a definite dose-response relationship with adverse responses[63] Gastrointestinal symptoms of nausea, vomiting and anorexia were more common with the larger dose, along with early neuropsychiatric responses of dizziness and fatigue.

With the increasing availability of artemisinin derivatives, treatment of complicated cases of malaria were investigated using artesunate with mefloquine. In 1990, at the Bangkok Hospital for Tropical Diseases, 24 recrudescent falciparum malaria cases were treated with sequential artesunate followed by mefloquine[64,65] The sequential treatment method was used specifically to avoid side effects from interactions. The regimen was well tolerated and completely effective with rapid parasite clearance and no recrudescence.

In an expansion of the research at the same hospital, two additional blinded control groups were added receiving either artesunate or mefloquine in the treatment of uncomplicated falciparum malaria[66,67] The recrudescence rate had been recorded at 50% in the area and "cure" in the study was defined as no recrudescence (by definition, after 28 days). Cure rates were above 80% for the single treatment regimens (artesunate 35/40, mefloquine 30/37) and complete for the combination (n=39). However, gastrointestinal adverse events, particularly nausea and vomiting were more common, but not significantly so, in the combination group compared to single therapies. In a subgroup investigated for pharmacokinetic interactions, artesunate increased the clearance rate, decreased the maximum concentration and expanded the volume of distribution of mefloquine[68]

With a similar combination used in Myanmar against complicated malaria for which the mortality rate following treatment with quinine was 8.5%, artesunate and mefloquine were not only completely effective, but also well tolerated by seriously ill patients[69] However, a single dose of artemether (300mg) followed by mefloquine (either 750mg or 500mg), caused nausea, vomiting and diarrhoea more commonly among Thai patients (n=159) treated for resistant falciparum malaria compared to those treated with artemether alone[70] These findings were similar to other studies of artemether (300mg) followed by mefloquine (750mg) compared to an additional dose of mefloquine (500mg) 12 hours later[71] When artemether was replaced with artesunate in the combination with mefloquine, for the treatment of Thai males with malaria, adverse events were not significantly different to those from artemether alone[72,73] Artesunate was well tolerated in a wider Thai sample including children and females and over longer courses in combination with large bolus doses of mefloquine (25 mg/kg)[74]

The additional adverse effects of mefloquine immediately following artemether is probably small as artemether alone[a] has been found to have no fewer adverse events than the combination of artemether (300mg) with mefloquine (750mg) administered on the next day[75] Also, artesunate suppositories followed by mefloquine are well tolerated by severely ill malaria sufferers[76,77] Artemether[b] or artesunate[c] in combination with mefloquine (25mg/kg) compared directly to mefloquine (25mg/kg) alone for the treatment of multi-drug resistant falciparum malaria on the Thai-Myanmar border, were equally well tolerated and more effective[78]

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[a] Artemether 400mg bolus with 100mg daily for three days

In Africans with falciparum malaria (n=38)[79], artemisinin alone[d] was compared with the combination of artemisinin[e] and mefloquine[f]. One serious adverse event, a seizure, was recorded in the combination group. While maximum plasma concentrations of artemisinin and elimination half-lives were comparable between the two groups, the area under the artemisinin concentration time curve was higher in the group given the drug combination. The combination of artemisinin and it's derivatives with mefloquine is commonly recommended to prevent the development of artemisinin-resistant malaria[80]

The combination of artemether with benflumetol followed the establishment of the artemisinin/mefloquine combination. In 1996, an open randomised trial for the treatment of multi-drug resistant malaria on the Thai-Myanmar border, the adverse responses to the artesunate-mefloquine combination were two to four times more common than for artemether-benflumetol[81] The adverse events included nausea, vomiting, dizziness, sleep disorders and neurological sequelae. With impressive efficacy, this combination may replace the use of mefloquine in treatment of resistant malaria. Also appearing for the treatment of malaria is Malarone™ (a fixed combination of proguanil 100mg and atovaquone 250mg). Malarone™ (four tablets daily for three days) has also been found to be more effective than mefloquine[g] in an open label randomised clinical trial, with a similar side effect profile including anorexia, nausea, vomiting, diarrhoea and cough, though vomiting was more common

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[b] Artemether 4mg/kg/day for three days
[c] Artesunate 4mg/kg/day for three days
[d] Artemisinin 500 mg two doses on the first day, then single dose followed by 250 mg twice daily for 4 days
[e] Artemisinin 500mg then 750mg in the first 24 hours, then 250mg three times in the next 24 hours
[f] Mefloquine 250mg three times in the first day

in the mefloquine group[82]. These adverse responses appear consistent across several therapeutic trials against other antimalarial agents[83] including in the face of multi-drug resistant malaria[84]

Neuropsychiatric Adverse Effects

Adverse effects of the central nervous system collectively are known with several classes of antimalarial drugs, particularly quinoline and artemisinin derivatives. While the terms are used inconsistently and rather loosely in scientific literature, they are taken here as neurological, including electrophysiological effects, being organic in nature; or neuropsychiatric. Notably, these adverse events associated with mefloquine (1/10000) are probably comparable to chloroquine (1/13000)[22] which was initially thought too toxic for human use before becoming the mainstay of treatment and prevention for 40 years[21] Additional risk factors for central nervous system adverse effects are pre-existing medical history, racial factors (Caucasian), repeat treatment and treatment with two agents from the same class[85]

Specific trials of mefloquine by Struchler et al (1990) and Held et al (1991) in the treatment of falciparum malaria in South East Asia were conducted with particular reference to the neuropsychiatric effects[86,87] Both studies demonstrated neuropsychiatric adverse events, essentially moderate to severe central nervous system symptoms in patients treated with mefloquine. Similar findings arose from neuropsychiatric studies on Africans receiving mefloquine for treatment of malaria[88]

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[g] Mefloquine 750mg followed by 500mg six hours later

Major adverse responses to mefloquine were also described in treatment of Europeans with acute falciparum malaria. A Germany study[89] attempted to define the relative incidence of major adverse responses between mefloquine treatment and prophylaxis. The study concluded that all neuropsychiatric adverse responses from sleep disturbance to psychosis or seizures were 60 times more common when mefloquine was used in the treatment of acute falciparum malaria (risk = 1/215) compared with chemoprophylaxis against malaria (risk = 1/13000).

Initially, anecdotal cases were reported of neuropsychiatric events wit the use of mefloquine. Caillon and colleagues in reported a case of initial insomnia with a depressive illness in 1992[90] This was followed by a case series collected illustrating acute psychoses with visual and auditory hallucinations along with sleep disorders associated with mefloquine treatment[91] Adverse responses were noted to reverse within weeks of prophylaxis or treatment being ceased[92].

Other electrophysiological effects

Mefloquine does not produce prolongation of ECG intervals or alter cardiac contractility in vivo[93], although, electrophysiological adverse responses have been described by Laothavron et al (1992) in a series of acute malaria cases being treated with mefloquine[94] These malaria cases (n=102) had uncomplicated falciparum malaria and were treated at the Department of Medicine, Pramongkutklao Hospital and Medical College, Bangkok, Thailand, with between 750mg and 1250mg mefloquine. A further 18 healthy males received 750mg of mefloquine as control subjects in the trial. Sinus bradycardia was recorded in 61% and sinus arrhythmia in 45% of subjects, although, these were all considered asymptomatic and did not occur

at the time of peak mefloquine concentration peaks between 12 and 24 hours after administration. They were also more common among patients compared to healthy volunteers. The conclusion drawn was that mefloquine was unlikely to have cardiotoxicity.

This hypothesis was tested in a series of field studies in the treatment of uncomplicated falciparum malaria with mefloquine among the Karen people of the border regions of Thailand and Myanmar. In a large study of 437 malaria cases, mefloquine 25mg/kg was less effective and less well tolerated than even high dose halofantrine (72mg/kg)[95] Conversely, in a smaller study on the same group, the same mefloquine dose was not found to have any adverse electrocardiographic responses (n=53), whereas the high dose halofantrine induced PR and QT prolongation in all patients (n=61)[96]. Notably, seven of ten patients re-treated with halofantrine after treatment failure with mefloquine rapidly developed QT prolongation. The findings of halofantrine-induced QT prolongation (period of cardiac ventricular depolarisation) aggravated by mefloquine have subsequently been demonstrated elsewhere[97] A similar concern for the use of mefloquine followed by treatment of malaria with Co-artemether[h], was dispelled by a well-designed study demonstrating no electrocardiographic changes with sequential treatment[98].

All gastrointestinal, neuropsychiatric and electrophysiological adverse responses following mefloquine treatment should be placed in the perspective of the alternative treatment for complicated falciparum malaria. The alternative is quinine, which causes cinchonism (tinnitus, high-tone hearing impairment, nausea, dysphoria and

[h] Artemether 20mg with Lumefantrine 120mg, used as six tablets four times over 60 hours

vomiting) in a high proportion of patients[99,100] Only 12% of patients receiving mefloquine experience cinchonism (less than with quinine), which is uncomfortable and may require poly-pharmacy to manage[101].

Adverse events from treatment with mefloquine - conclusion

The differences between the clinical manifestations of complicated malaria may be difficult to discern from those iatrogenic consequences of mefloquine treatment[102] For groups such as children, mefloquine may be very controversial and may almost be relied upon to make the patient more ill, although, ultimately prevent death from multi-drug resistant malaria[103]

Perhaps the ultimate investigation of mefloquine treatment of malaria, at least in Asian patients, was conducted from 1990 to 1994 in Thailand[104] The Faculty of Tropical Medicine, Mahidol University, catalogued 3673 patients aged between 6 months and 88 years treated with between 15 and 25 mg/kg mefloquine. The primary comparison was mefloquine dose. Anorexia, nausea, vomiting, dizziness and sleep disorders were significantly more common with the higher dose of mefloquine. Splitting doses and delaying mefloquine dose when administered in combination with artemisinins reduced adverse response. Abdominal pain, diarrhoea and headaches were associated with mefloquine.

Any adverse events associated with mefloquine will be influenced by experience and observation bias. There is much controversy about mefloquine adverse responses. The extent to which this influences the reporting of mefloquine adverse responses may be demonstrated in a combination prospective and retrospective study by Ronne

et al (1998) of adverse responses observed in patients being treated for malaria. While the three year prospective study recorded adverse events from 96% of patients including 28% with one or more neuropsychiatric reactions, the retrospective study over a comparable period and population register reported no neuropsychiatric reactions[105] The conclusions drawn were that "one finds what one looks for" Prospective and retrospective studies may give different results and the relatively infrequent nature of neuropsychiatric events may contribute to these effects.

Adverse events associated with mefloquine prophylaxis for malaria

While the predominant initial research on mefloquine adverse events was derived from treatment trials and from post-registration observations of therapy, prophylaxis is the more common mode of use of mefloquine. Prophylaxis uses lower dosages to treatment and therefore has a lower incidence of adverse event profiles. The recommended malaria prophylaxis regime with mefloquine for travellers is 250mg weekly beginning prior to entry to the malarious area and continuing for two to four weeks after[106,107] This is the case in Australia where mefloquine is recommended for use in areas with chloroquine-resistant malaria, though not in areas with mefloquine resistance[108] The mefloquine dose was originally derived from approximately 7mg/kg fortnightly[109] which is markedly less than treatment regimens using 15-25mg/kg as a bolus dose or split regime within a 24-hour period[15]

The earliest clinical trials of mefloquine against sporozoite-induced malaria illustrated the potential for the agent to be effective in chemosuppression of human malaria[36] Chemosuppression of malaria suggested an appropriate use for mefloquine would be

for prophylaxis against malaria for non-immune travellers passing through malarious areas. Mefloquine was effective against known resistant strains given experimentally to non-immune volunteers without any adverse responses reported[37] This feature immediately placed mefloquine as a suitable alternative for chemoprophylaxis in areas of chloroquine-resistant endemic malaria. However, early large-scale field trials comparing mefloquine to a fixed sulfadoxine-pyrimethamine combination[109] identified possible "quinine-like" adverse events.

The first large post-registration comparison of mefloquine in prophylaxis was as MSP (a fixed drug combination of 250mg mefloquine, 500mg sulfadoxine and 25mg pyrimethamine). In a randomised double-blind trial by Kollaritsch et al (1988), 110 Austrian expatriates to Nigeria working in Nigeria were given chloroquine 300mg base weekly and 101 were given one MSP weekly[110] Seven volunteers ceased MSP and two withdrew from chloroquine prophylaxis. Adverse responses were thought to be due to the mefloquine component, though the study could not demonstrate this. Effects included insomnia, palpitations, dizziness, nausea and headache. This trial was not large enough to determine efficacy.

The prophylactic effectiveness of MSP was investigated by Kamolratanakul et al (1989) in a double blind controlled trial of 193 non-immune migrants living in a highly malaria endemic are of eastern Thailand[111] The control group received 12 weeks of Fansidar. The conclusions drew attention more to the potential adverse outcomes associated with long term use (12 weeks in this trial) of long acting sulphonamides than complete malaria suppression with MSP compared to eight breakthroughs on Fansidar. A similar study was repeated in Malaysia with larger

numbers (n=914) with random allocation to one of two doses of MSP or Fansidar, adverse events were noted to be largely abnormal blood chemistry and to be lesser with the lower dose[112]

Field studies by Reisinger et al (1989) using mefloquine alone in the form of Lariam™ for prophylaxis compared to MSP demonstrated gastrointestinal and autonomic nervous system adverse responses, including liver enzyme anomalies for both drugs[113] From this randomised double-blinded trial of 193 travellers, one volunteer withdrew from Lariam™ prophylaxis and two from MSP. Guarded use was recommended for travellers with known liver dysfunction. Interestingly, mefloquine-resistant *P. falciparum* developed in one volunteer who had travelled to West Africa. This was treated successfully with chloroquine.

Shanks et al (1989) at the Armed Forces Research Institute of Medical Science (AFRIMS) in Bangkok reported[114] the growing problem for the Royal Thai Army of malaria resistant to chloroquine and pyrimethamine/sulfadoxine. They then described the use of mefloquine and doxycycline with cautions on use due to the complexity of factors involved.

The appearance of multiple drug-resistant malaria in Thailand had prompted the use of doxycycline for chemoprophylaxis[115,116,117] Pang et al (1987) investigated doxycycline for malaria prophylaxis in 188 school children aged 10-15 years living along the Thai-Myanmar border[118] Of the 95 children receiving doxycycline, five developed falciparum malaria which was considered a better outcome than the 93 children receiving adult doses of chloroquine and suffering 31 cases of falciparum

malaria. Gastrointestinal adverse events were considered comparable. Use of doxycycline in children was not limited to studies in Thailand as it was used to clear malaria from 190 students in the Rift Valley (Africa) with amodiaquine before a trial of proguanil and bed nets[119]

Doxycycline was established as an emerging chemoprophylaxis agent for malaria in military populations when AFRIMS demonstrated greater suppression from both 50mg and 100mg daily doxycycline compared to the fixed drug combination of pyrimethamine/dapsone (Maloprim^{TM}) used by Royal Thai Marines on the Thai-Kampuchean border[120] A notable secondary finding was comparable compliance between daily doxycycline and the weekly Maloprim^{TM}

As comparisons grew between doxycycline and mefloquine, the possible benefit of protection against enteric infections with doxycycline was addressed. A double-blind study of the daily and weekly regimens was conducted by Arthur et al (1990) in US soldiers on exercise in Thailand[121] In this group, the first large-scale quality comparison of the chemosuppression agents was conducted without demonstrating any great difference in consumer acceptance or efficacy[122]

The Centers for Disease Control and Prevention (CDC) published recommendations of mefloquine for chemoprophylaxis for travellers to areas with known or suspected chloroquine-resistant falciparum malaria, which were considered to be most areas with malaria[123,124] The CDC also altered dosage recommendation to maintain weekly prophylaxis during exposure and for up to four weeks after leaving the malarious area[125] Yet, the progressive accumulation of real and supposed adverse events to

mefloquine was prompting recommendations for restricted use only for specific indications in areas of known high-level chloroquine-resistant falciparum malaria[126] and reports of failure of suppression were appearing[127,128].

Other regimens of mefloquine prophylaxis were investigated. Tolerance of half dose (125mg) weekly mefloquine was not significantly different to that of half dose MSP, full dose Fansidar[i] or chloroquine 300mg, each given weekly[62] Bunnag et al (1992) administered one of these chemoprophylactic drugs was received by Thai volunteers (n=602) living on the Kampuchean border, in a randomised double-blind placebo controlled trial over 24 weeks. An alternative weekly regimen was tried using 500mg mefloquine (n=145) in comparison to Fansidar combined with chloroquine 300mg weekly (n=112), and chloroquine 300mg alone weekly (n=77)[129] Mefloquine prophylactic efficacy (79%) exceeded that of Fansidar and chloroquine (18%). There were no remarkable differences between tolerance of each regimen. In a related pharmacokinetic study, the higher dose of mefloquine (500g) was found to cause adverse events in two of six volunteers[130] Both experienced nausea after the first 500mg dose which did not continue with the subsequent four weekly doses. Despite acceptable tolerance, the absorption half-life of 6.6 hours (+/- 3.0 hours), the terminal half-life of 12.9 days (+/- 2.2 days) and (individual) mean minimum plasma mefloquine concentrations from 290 to 460ng/ml suggested suppression would be regularly inadequate therefore a weekly regimen was recommended. This was confirmed by the CDC sponsored Peace Corps trials in West Africa that demonstrated suppression breakthroughs occurred in the second week after dosing with alternate

[i] 500 mg sulfadoxine + 25 mg pyrimethamine

week mefloquine (250mg)[131] Non-suppressive blood levels were identified in these cases and the trial formed the foundation for the CDC policy referred to above.

As soon as weekly mefloquine was established as recommended long-term prophylaxis, the three-week elimination half-life raised concerns of accumulation and toxicity. An extended pharmacokinetic investigation of 15 Canadian travellers using mefloquine prophylaxis weekly over a three-month period did not show toxic accumulation and confirmed significantly higher trough levels with weekly over alternate weekly dosing[132] In a larger pharmacokinetic study of mefloquine, involving Columbian workers taking either Fansidar weekly or Lariam on alternate weeks for six months, a 26 day half-life was found for mefloquine. The authors concluded that the regimen could be used safely for several years[133]

More military trials of mefloquine for chemosuppression were conducted with the Royal Thai Marines Militia operating on the Thai-Cambodian border[134] Troops were intended to receive weekly mefloquine 250mg, however, analyses using receipt of two or more doses per month for outcomes and reported 91% compliance with no neuropsychiatric reactions.

In 1992, the International Drug Safety Department of F. Hoffmann-La Roche released findings of reported spontaneous drug reactions associated with mefloquine[135] Of 59 serious neurological and psychiatric adverse responses in the six years after mefloquine availability, 26 convulsions, 12 acute depressive illnesses, 20 acute psychotic episodes and one toxic encephalopathy were included, none of which were fatal. After identifying that these were consistent with other quinine-derived

antimalarials, it was recommended to restrict prescribing to those patients with history of seizures or manic-depressive illness. Nevertheless, by this time mefloquine was considered to be contraindicated for nine percent of travellers prepared by travel clinics in the United States[136]

Despite the apparent large numbers of adverse events associated with mefloquine, in specific chemoprophylaxis field trials, tolerance was as good as alternatives, particularly chloroquine. The CDC expanding work with the Peace Corps in East Africa demonstrated that not only was mefloquine 250mg weekly (in the form of Lariam) more effective than weekly chloroquine (300mg), it was as well tolerated[137] Minor adverse events were recorded with the same frequency in both arms of the study.

Other field trials measuring real-time tolerance of mefloquine in Africa supported these findings. In-flight questionnaires completed by 145003 travellers returning from Kenya to Europe, indicated that antimalarial drug side effects were generally mild[138] Those side effects arising from mefloquine (18.8%) were more common than from sulfadoxine/pyrimethamine, but, no more common than for chloroquine 300mg (17.1%) or 600mg (18.6%) weekly and less frequent than from weekly chloroquine with daily proguanil (30.1%).

The simplicity of mefloquine chemoprophylaxis for travellers in addition to the findings of tolerance and effectiveness generated arguments for exclusive use in all areas except the Thai borders with Myanmar and Cambodia[139] In 1994, the matter of mefloquine-resistant falciparum malaria was well identified at this time along with the

possible contribution of inappropriate drug use in areas such as the border regions of Thailand[140,141,142]

Confusion among both travellers and prescribers was supported in a study of German travellers contracting malaria on returning home[143] Only 3% of patients had used the correct chemoprophylaxis for their exposures. The effect was comparable in North America as up to 60% of travel health advisers were shown to prescribe incorrect malaria chemoprophylaxis[144]

Nevertheless, the unqualified recommendation by Lobel and Keystone[139] was challenged as an oversimplification of chemoprophylaxis for chloroquine-resistant malaria endemic areas[145] Arguments included the lack of proven safety in special groups such as children and pregnant women. Furthermore, it was countered that safety for unqualified recommendations could only be made on prospective trials, which were lacking, and that conclusions based on airline passenger questionnaires were of questionable validity. These are salient arguments summarising the issues around mefloquine chemoprophylaxis. Continued consideration of clinical status, risk of adverse reactions, risk of infection, length of exposure and geographic region were recommended. Further comment emphasised the individual differences of every traveller and their travel and the folly of dogmatic regimen recommendations[146]

The simplification of malaria chemoprophylaxis contradicted the concerns and findings of the time regarding neuropsychiatric adverse events. French travellers to Senegal prescribed chloroquine and proguanil chemoprophylaxis had no more adverse events overall than those travelling to Kenya using mefloquine chemoprophylaxis but,

non-serious neuropsychiatric events were more frequent among the travellers to Kenya[147] A telephone survey of British civilian travellers found an increase in intermediate level neuropsychiatric adverse events from mefloquine chemoprophylaxis[148] Again, overall adverse events from mefloquine chemoprophylaxis were no more common than with chloroquine and proguanil (both 40%).

British travellers were not at this time unbiased in their opinions of mefloquine. In the United Kingdom, mefloquine had begun to develop media attention that translated into reduced sales by Roche[149] Travellers using mefloquine were more likely to report adverse events having been exposed to related media coverage. Even though sales were falling associated with specific media coverage events, the overall use of mefloquine since introduction in Britain had apparently reduced the incidence of imported malaria from Kenya to one third of previous levels[150]

A double-blind placebo-controlled healthy volunteer study of mefloquine adverse events by Davis et al (1996) refuted the hypothesis that mefloquine was related to low-grade neuropsychiatric events even though it may be associated with other electrophysiological phenomena when taken as a prophylaxis[151] This study included active investigations regarding cerebral function. The study was conducted with healthy Australian staff and students from a teaching hospital in Perth, excluding those with a history of psychiatric, neurological, cardiac, hepatic or renal disease, pregnant or lactating women and those who had taken mefloquine in the preceding three months. Unfortunately, the sample size of 95 volunteers completing the four-week period may not demonstrate uncommon adverse events. Similar findings were

generated by a group in Zurich also performing computerised psychomotor testing specifically on those recipients reporting adverse events related to mefloquine prophylaxis during travel to Africa[152] While 11.2% of participants reported adverse events including 7.9% neurological or psychiatric events, such as dizziness, distress, sleep and mood disturbances, no deficit could be demonstrated in testing.

The nature of chemoprophylaxis had been to provide one dose of mefloquine for one dose one week prior to departure and to continue for two to four weeks after leaving the malarious area[153] However, this regimen was called into question following reports of Dutch travellers contracting malaria in the Gambia. Several of the cases were confirmed as compliant with mefloquine because of serum levels present at the time of malaria diagnosis[154] The Gambia was known to be relatively free of mefloquine-resistant malaria leaving the conclusion that the pharmacology of mefloquine should warrant a loading dose prior to malaria exposure. The additional time for achieving suppressive levels was suggested to also allow familiarising travellers with the medication to improve compliance[155] Back extrapolation of mefloquine serum levels creates a potential bias as inter-individual variation in drug levels are large and that the levels of mefloquine found below that thought necessary for suppression[137] may be due to poor compliance[156] Further, loading doses had been recommended prior to the Gambia finding[157] though were not included in the package insert[158].

The hallmark study of civilian malaria prophylaxis acceptability in Australia was conducted through the Travellers Medical and Vaccination Centres in Melbourne and Adelaide[159] The comparison was made between mefloquine and doxycycline

chemoprophylaxis, as these were the options available to Australian travellers when embarking for areas, with known or possible chloroquine-resistant malaria. The sample size was large with 285 travellers eventually taking mefloquine and 383 travellers taking doxycycline. The duration of prophylaxis was relatively short, averaging only 6.5 weekly doses of mefloquine and 27.5 daily doses of doxycycline. The results need to be interpreted cautiously as selection into either group followed extensive discussion regarding use of the prophylactic agent. Of those taking mefloquine, 37.9% attributed symptoms experienced to mefloquine and 78.2% complied with the full course prescribed. Conversely, only 21.4% felt doxycycline caused symptoms, but only 68.1% complied with the course. Adverse events were more commonly reported by women which was consistent with other investigations involving European travellers[152]

Croft and Garner[160] conducted the first Cochrane Review of mefloquine for preventing malaria in non-immune adult travellers. Their findings revealed only ten randomised controlled trials which included 2750 non-immune volunteers. Four placebo-controlled trials were found to indicate higher withdrawals from the mefloquine regimen. However, while withdrawal rates were high across five studies that compared mefloquine with other antimalarials, the meta-analysis did not demonstrate a greater intolerance of mefloquine compared to other chemoprophylaxis regimens. The conclusions drawn were that mefloquine has adverse effects which should limit use to prophylaxis for certain groups, such as the military travelling to chloroquine-resistant malaria endemic areas. Notably, of the 516 case reports of mefloquine (chemoprophylaxis) adverse events, most (63%) involved tourists and business travellers, not military personnel. Yet the only studies included by the

reviewers in which mefloquine was used for chemoprophylaxis in malarious areas was conducted in military personnel.

Mefloquine prophylaxis with concurrent medication

Whether mefloquine causes more adverse events compared to other antimalarials has a clear confounding variable from concurrently consumed medications. In most reported studies, the use of concurrent medications were generally implicitly (or through omission) assumed to be equivalent between cohorts. As travellers are likely to use polypharmacy for either prevention or treatment of intercurrent travel-related illness, there is a real need to control for this potential bias. A database by Handschin et al (1997) previously collected to compare adverse events of chemoprophylaxis agents including concurrent medication was reanalysed with regard to polypharmacy[161] Reporting adverse events was more common when co-medication was also reported, especially severe adverse events. The medication most associated with reported adverse events were neuropsychiatric agents and the least associated were cardiovascular agents. Overall, co-medication with mefloquine was not associated with more reported adverse events than with chloroquine.

A specific subset of co-medication among travellers is the use of illicit or recreational drugs. A subsequent investigation of younger travellers (n=1340) demonstrated an increased risk of neuropsychiatric adverse events with the use of mefloquine chemoprophylaxis, although, 22.2% of the group admitted to using recreational drugs while travelling and another 12% failed to complete this question[162] The nature of the recreational drugs was not defined.

Another situation of concurrent medication used by travellers is during the pre-travel preparation with vaccines. Prevention of travel-related hepatitis A and typhoid are probably not cost-effective, at least for British travellers[163] Conversely, malaria chemoprophylaxis with either chloroquine or mefloquine is cost-effective and commonly begun at the time of pre-travel vaccination. Mefloquine or chloroquine consumption at the same time as oral live cholera vaccination (CVD103-HgR) reduces vibriocidal antibody titres[164] Only proguanil reduced the anti-Salmonella typhi lipopolysaccharide antibody response from concurrent oral typhoid vaccine (Ty21a). The converse influence of vaccines on the efficacy of antimalarials has not been measured, nor the influence of concurrent vaccines on reporting of adverse events attributed to antimalarial agents.

Military chemoprophylaxis with mefloquine

The British Army policy for malaria chemoprophylaxis for exercises in central Kenya used chloroquine 300mg weekly and proguanil 200mg daily. This policy was reassessed following seven cases of malaria sustained among only 150 soldiers during an exercise in 1992[165] Even though chemoprophylaxis compliance was not directly assessed, the policy was changed to simplify the regimen to mefloquine 250mg weekly.

The British Army policy change was interesting in that the experience of the Dutch military was not favourable towards mefloquine. Three Dutch Battalions of Marines had suffered 31 *P falciparum* infections during their deployment to Cambodia over 1992-3 on mefloquine chemoprophylaxis[166] Although the Dutch were operating in areas of potential endemic mefloquine-resistant falciparum malaria, compliance was

only 86% and 30% of the Marines reported adverse events. The Dutch concluded that it was nevertheless "well tolerated" though not totally effective after detailed surveillance of the final group[167]

For the British, Croft[168] made the point that mefloquine toxicity was comparable to other forms of chemoprophylaxis in use. He later demonstrated that the incidence of severe neuropsychiatric events is less than 1:6000 soldiers exercising in Kenya[169] and that on exercise, British soldiers do not report any more adverse effects from mefloquine than on the combination of chloroquine and proguanil[170]

More information about the use of mefloquine under military operational conditions began to arise when significant unrest in East Africa drew military peace-keeping operations into the malarious area. Between December 1992 and May 1993, 9000 US troops were deployed to Somalia sustaining 48 non-battle casualties from malaria[171] Risk factors identified were non-compliance with chemoprophylaxis including both doxycycline and mefloquine. Mefloquine effectiveness in the region was incomplete as five casualties were found to have suppressive serum mefloquine levels on diagnosis of malaria. Similar findings on those with doxycycline are probably not relevant as recent use and the short half-life would produce suppressive levels even though prior to infection these had not been sustained. One year after the operation had begun, the US military had imported 112 cases of malaria[172]. On interview, 56% of these cases reported compliance with chemoprophylaxis, however, 50% of the group interviewed had been prescribed an inadequate dosage regimens of doxycycline or mefloquine.

The Italian military operating in Somalia fared better with only 18 casualties from malaria among 11600 soldiers deployed using chloroquine 300mg weekly and proguanil 200mg daily[173] These were pleasing results in light of the British experience in Kenya[165] However, chloroquine with proguanil began to fail the Italian forces as they sustained 100 malaria casualties in the first three months of deploying 4800 soldiers into Mozambique for peace-keeping operations in 1992. They responded with a similar change in chemoprophylaxis policy to the British, employing mefloquine 250mg weekly. This contributed to limiting the subsequent malaria non-battle casualty total to 19 casualties in the remaining two months of the operation[173] A subsequent review of these two operations collectively involving 5120 Italian soldiers supported mefloquine chemoprophylaxis as easier to comply with and not associated with a greater discontinuation rate than chloroquine and proguanil chemoprophylaxis[174]

Brazilian peacekeepers deployed to Angola for six months in 1995 to 1996 using mefloquine 250mg weekly for malaria chemoprophylaxis[175] Despite the regimen, 78 of the 439 personnel contracted clinical malaria. An outbreak investigation was conducted in collaboration with the US military. The conclusions were that a newer, more efficacious chemoprophylaxis agent was needed for military forces, despite the finding of poor and erratic compliance as the major risk factor for malaria.

In another collaboration with the US military, non-immune Indonesian soldiers posted into Irian Jaya from non-malaria endemic regions of Indonesia were provided with mefloquine 250mg weekly and doxycycline placebo, doxycycline 100mg daily and mefloquine placebo or only placebo tablets for the first three months of posting[176]

The Indonesian soldiers tolerated mefloquine chemoprophylaxis well and experienced complete efficacy with the regimen. Notably, mefloquine was not open label on this trial. This is comparable to the findings of earlier studies by the US AFRIMS group with the Royal Thai Marines on the Thai-Kampuchean border with whom mefloquine was well tolerated and compliance readily achieved (91%)[134]

The Australian military experience with mefloquine is relatively short and limited as doxycycline 100mg daily has been the main chemoprophylaxis regimen since replacing chloroquine and Maloprim in the early 1990's. Transfer to doxycycline 50mg daily in combination with chloroquine 300mg weekly followed increasing failure from the combination regimen employed under field conditions in Papua New Guinea[177] Various combinations of chemoprophylaxis were considered and tested including mefloquine 250mg weekly which was found to be completely effective in protecting a small group soldiers against falciparum malaria. However, without using primaquine terminal prophylaxis to address liver stages of the parasite, vivax malaria occurred on return to Australia.

Mefloquine was established as the first alterative to doxycycline 100mg daily for short-term exposures in malaria endemic areas[178] It was used in this capacity for those intolerant of doxycycline during Australian deployments to Cambodia and Somalia and exercises to Papua New Guinea, though numbers of personnel using the regimen were very small[179,180]

Chapter 3 – Methods

Justification for the study

There is clear evidence of adverse events and non-compliance with mefloquine chemoprophylaxis in smaller studies on military populations but no large studies conducted on Australian soldiers under field conditions define the adverse event profile.

At the time of planning for this study, a large (blinded) trial involving mefloquine as a control for new weekly antimalarial was being conducted. While this trial did not use open label mefloquine chemoprophylaxis, the preliminary evidence suggested the regimen was an effective and well-accepted chemoprophylaxis for the ADF under operational conditions. From early studies with Australian soldiers in East Timor, the acceptance levels and effectiveness of doxycycline left scope for improvement under these conditions.

Objective

The objective of the study is to define the adverse events of mefloquine (particularly the predictability) and compare these with those of doxycycline.

Hypotheses

H_0: Reported $AE_{mefloquine}$ = Reported $AE_{doxycycline}$

H_0: Initial $AE_{mefloquine}$ = Steady state $AE_{mefloquine}$

Ethical approval

Ethical approval for the study was obtained from the Australian Defence Health Research Ethics Committee.

For all research on Australian Defence Force personnel the Australian Defence Health Research Ethics Committee (ADHREC) must be consulted. Research may require ethical approval by this body. Clinical trials will require both consideration and ethical approval from ADHREC. Submission of results to ADHREC and for peer review in scientific meetings and journals is mandatory and contingent for approval by the Committee.

This committee sits quarterly, chaired by the Surgeon General of the Australian Defence Force, Air Vice Marshall Bruce Short FRACP.

Two ADHREC meetings were attended to present the proposed research clinical trial protocol, address concerns and amendments. The Committee had significant reservations about this protocol. The major concerns were the possibility of neuropsychiatric adverse events arising among armed volunteers in the sensitive circumstances of peacekeeping. Specifically, these adverse events were considered unacceptable when experienced by personnel handling loaded weapons and in command of vehicles. Given the sensitive nature of peacekeeping in the months after stabilisation of the land border area of East Timor, any behavioural abnormality whether or not involving weapons was also considered a risk to use of mefloquine chemoprophylaxis. Further concerns were held regarding disclosure of possible

adverse events as soldiers may weigh the commitment to continued service on operation as greater than the need to report adverse events that may potentially result in their temporary or permanent withdrawal from the operation.

Mefloquine 250mg weekly is registered in Australia for chemoprophylaxis against malaria, with only one dose prior to departure. It is also the first alternative after doxycycline in the Defence Health Policy Directive (215) published by the Health Service Branch of the ADF. This trial offered the prospects of specific evidence behind the policy.

The Committee accepted the likely predictive nature of observing four doses prior to deployment. It also required disclosure of all adverse events associated with mefloquine including to "rare" adverse events as defined by MIMS Annual, 2000. Appropriate amendments were made in the protocol and approval was granted.

Attached at Annex D are:

Members of the ADHREC

ADMEC Minute DHSB 320/2001 – provisional approval for the study

ADMEC Minute DHSB 1127/2001 – acceptance of amendments

Study Design

The study design was an open clinical trial. Volunteers of the core elements of the Battalion group were given a loading dose of mefloquine followed by three weekly doses pre-deployment in accordance with HPD215. A further sub-population (Company size) was randomly selected for more detailed investigation. The remaining non-core elements of the Battalion group were provided conventional chemoprophylaxis in accordance with HPD215, viz. doxycycline 100mg daily.

The Company sub-group selected underwent pharmacokinetic studies at key intervals throughout the deployment. These key intervals include following loading dose, during a patrol period (high workload and intense field conditions), and prior to redeployment to Australia.

All core elements of the Battalion group were supervised using a log return system of reviewing compliance with chemoprophylaxis as recorded by responsible individual, generally the Platoon Sergeant. Questionnaires were delivered requesting information regarding adverse events at key intervals including following loading dose, midway through the deployment and prior to return to Australia.

Study Population

The study population included the core elements of the forward Australian Battalion groups deploying to East Timor under Operation Tanager during the period April 2001 and October 2001. The core elements of the Battalion group included the four Rifle Company and attachments, Headquarter elements, Administration Company and Support Company groups. Other Battalion group attachments remained on

chemoprophylaxis in accordance with HPD215 and were monitored with existing surveillance systems.

a. Inclusion Criteria: To be included in the study the trial volunteer must:

i. Be male or female between 18 and 55 years of age;

ii. Be Medical Class 1 or 2; and

iii. Be willing and able to give written informed consent and comply with the study protocol.

b. Exclusion Criteria: Volunteers will be ineligible for inclusion into the study if any of the following applies:

i. They are pregnant or unwilling/unable to comply with recognised contraception methods (abstinence, oral contraception or barrier methods) for 30 days after administration of the study drugs;

ii. They have a known hypersensitivity to any component of the study drugs;

iii. They are unwilling/unable to give blood collections required in the study;

iv. They are taking any other investigational drug during, or within 30 days, of taking the study drugs for this study.

As the ADF policy (HPD 215) does not specify other contraindications, no further exclusion criteria were used.

Volunteer Consent

Volunteers were recruited using non-coercive means. No inducement will be offered. Volunteers who are invited to take part in a clinical trial were entitled to make a choice based on full and complete information presented in a manner understandable and ethnically appropriate. The Information and Consent Form was designed to assure the protection of the volunteer's rights.

The volunteers were informed of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it may entail. In addition, a copy of the Information and Consent Form was provided which outlines this detail. The volunteer was given every opportunity to clarify any points that he/she may not understand and to seek additional information. The volunteer retained the right to withdraw from the study at any time without penalty.

The informed consent was recorded in writing with the investigator and the volunteer both signing and dating the Information and Consent Form.

The signed Information and Consent Form is retained with the original case record form (CRF).

The Consent Form Protocol is attached as Annex E.

Withdrawal of Volunteers

Volunteers may withdraw themselves or be withdrawn from the study at any time without prejudice or compromise to appropriate treatment or chemoprophylaxis or detriment to military career. Volunteers were withdrawn from the study if they experience significant adverse events to the study medicine, or if concomitant illness is likely to compromise their physical well being or their participation in the study. Reasons for withdrawal were recorded in the CRF If withdrawal was due to an Adverse Event then an Adverse Event Form was completed.

Quality Procedures / Assurance

a. Outcome Measures*:* The outcome measures are response to delivered questionnaires on adverse events and compliance, identified log returns on compliance and a positive malaria blood smear confirming clinical malaria.

b. Safety Parameters*:* Safety parameters established for the trial are the monitoring of:

i. Routine clinical laboratory tests (haematology and biochemistry) on a representative sample following loading dose reviewed by the investigator;

ii. Adverse events as per outcomes; and

iii. Pregnancy testing

c. Clinical Trial Material: All mefloquine was provided through the ADF Supply system using conventional distribution methods.

Laboratory Procedures

Whole venous blood was collected by venepuncture. Each sample was collected in 5ml Lithium Heparin tubes or SST tubes, with no more than 30mls of blood being collected for this study.

Procedures included:

a. Measurement of Parasitaemia - Thick and thin blood films for malaria obtained from a venous sample to confirm malaria as required by clinical examination. A confirmed instance of positive parasitaemia was considered a failure of chemoprophylaxis.

b. Haematology:

   i. Haemoglobin;

   ii. PCV (Haematocrit);

   iii. Platelets;

   iv. Total White Cell Count;

   v. Lymphocyte Count.

c. Biochemistry:

   i. Sodium;

   ii. Potassium;

   iii. Albumin;

   iv. Urea;

   v. Total Bilirubin;

   vi. Alkaline Phosphatase.

d. Pharmacology Venous Blood Sampling Schedule - Venous blood samples were collected following loading dose and at intervals throughout the deployment as outlined above.

All blood samples were centrifuged at 2,000 rpm for 15 minutes. Plasma was separated and stored chilled then frozen until thawed and analysed. Sera was stored and transported chilled only. Plasma concentrations of mefloquine were measured by HPLC at AMI.

e. Pregnancy Testing All volunteers of child bearing potential were questioned and tested for pregnancy at screening by urine testing techniques using standardised test kits. Although the dosing period is only 14 days maximum, women who believed they may become (or think they are) pregnant or who record a positive result on urine testing were excluded from the study.

Drug Dose

The study drug supplied (Mefloquine 250mg tablets as Lariam) was taken as follows:

a. Loading dose: 250 mg second daily for three doses in a week,

b. Predeployment maintenance: 250mg weekly for three weeks, and

c. Maintenance dose in AO: 250mg weekly.

Drug Storage, Inventory and Log Sheets

The conventional supply system for the Battalion group was utilised. Study drugs were stored according to the manufacturer's recommendations at ambient temperature (not greater than 25°C). A Platoon Non-commissioned Officer distributed the drug to

individuals weekly with the distribution logged in accordance with Formation Routine Orders. A clinical investigator collected log returns weekly.

Adverse Events

Volunteers had a history taken and physical examination performed whenever there are reported adverse events or experiences which are considered analogous. All adverse events were to be notified and discussed with the principle investigator within one week for a decision regarding continuation on mefloquine in consultation with the Regimental Medical Officer.

In the case of clinical malaria (one case), full clinical records from the treatment facility were obtained and the principle investigator consulted on the case personally.

Potentially lethal events and hospitalisation were considered serious adverse events (SAE) as deaths would have been had any occurred. These were notified to the principle investigator within 24 hours for a decision on continuation of the individual in the trial and on mefloquine in consultation with the Regimental Medical Officer or Health Support Battalion Senior Medical Officer.

Attached at Annex F are the Adverse Experience Guidelines from the ADMEC protocol 249/01

Attached at Annex G is the Adverse event record form

Concurrent Medication

If a volunteer developed an infection requiring treatment with antibiotics, the attending study clinicians were directed to prescribe an antibiotic without known antimalarial action (specifically excluding doxycycline and azithromycin). All other concurrent medication was recorded on the CRF

Implementation

Prior to deployment to East Timor on Operation Tanager in 2001, elements of the Fourth Battalion Group (approximately 900 personnel) were offered participation in a study of mefloquine used for operational malaria chemoprophylaxis. A description of the study followed an educational briefing on vector-borne disease delivered during preparation for deployment to East Timor. This briefing was conducted at the Shoalwater Bay training area during the pre-deployment exercise, "Exercise Timor Dawn" in April 2001.

During the presentation, the voluntary nature of inclusion was stressed to ensure recruitment was non-coercive. Those individuals choosing not to enrol were advised that this would not be detrimental to their career or deployment. As East Timor is a malarious area, they would receive doxycycline chemoprophylaxis for the deployment in accordance with the Australian Defence Force Health Policy Directive No. 215 - Malaria. After listing and discussing common, uncommon and rare side effects of mefloquine, those individuals with a history of anxiety or depressive disorders were advised against enrolling. These aspects were detailed and reiterated in the consent and information form.

Consenting volunteers fulfilling inclusion criteria of being Medical Class 1 or 2[j] were given a loading regimen (one 250mg mefloquine tablet second daily for three doses) then established on 250mg mefloquine weekly. Once established on weekly mefloquine, volunteers were given a supervised questionnaire to identify adverse drug reactions (ADR). The clinical investigators reviewed those reporting adverse events. Mefloquine intolerance at this and all subsequent times was managed primarily with alternative chemoprophylaxis using doxycycline (100mg daily as per the Australian Defence Health Policy Directive No. 215 – Malaria). Only one individual received proguanil and atovaquone (Malarone™) due to coexistent doxycycline intolerance. The Health Policy Directive (No. 215) directs use of Malarone as the next alternative for malaria chemoprophylaxis. Other adverse drug reactions not resolving rapidly were treated as clinically appropriate. All reported adverse events were recorded in the individual medical record and on the standard questionnaire. The clinical investigators assessed adverse events at the time of cessation of mefloquine to determine the relationship to the medication. All clinical information gained was included in the case record form.

Additional information from those volunteers not withdrawing from mefloquine and other volunteers questioned while taking doxycycline was gathered. Information on tolerability of mefloquine from volunteers was gathered on cohorts following the loading dose, approximately midway (greater two months after deployment and prior to August 2001) through the deployment in East Timor and during the repatriation process in the final days of the deployment in East Timor. A standardised

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[j] Medical Class 1: Fit for employment and employment in trade in any operational environment. Medical Class 2: Fit for employment and generally fit for deployment subject to a pre-deployment check based on geographic restriction or access to health support.

questionnaire was used. Questionnaires midway through the deployment were conducted in the forward area of operations. As a result, these were on an opportunity basis only being subservient to the operational contingencies. The final questionnaire during repatriation was delivered in association with the extraction medical interview. Questionnaires were completed by the soldiers prior to responses being reviewed during an interview with a clinical investigator. The Principal Investigator reviewed all significant responses immediately with the respondent and interviewer.

During the final extraction medical interview, those soldiers taking doxycycline were also questioned with their consent. The standardised questionnaire used for volunteers to the mefloquine study was used in the same manner.

Information from all questionnaires was collated on Microsoft Access. Odds ratios, confidence intervals and statistical significance between reported adverse drug reactions on doxycycline or mefloquine were analysed using Chi-square tables calculated on EpiInfo 2000 (Version 1.1, CDC).

Summary of the protocol and overview of study schedule is at Annex H.

Chapter 4 - Results

Sample

A total of 620 ADF volunteers started mefloquine including only two females. The recruitment and enrolment can be summarised as:

652 soldiers were included in the study of whom:

- 10 did not give consent (and were withdrawn thereafter),
- 22 did not deploy or did not start mefloquine (used doxycycline instead) and
- 620 who deployed using mefloquine chemoprophylaxis of whom
  - 527 completed the period of study on mefloquine and
  - 93 who withdrew from study including
    - 73 from adverse drug reactions (changed to doxycycline) and
    - 20 for other reasons.

367 individuals responded during the extraction phase of the operation, having used doxycycline chemoprophylaxis on the deployment.

Pharmacology

Two hundred and three volunteers who had been deployed for at least two months using mefloquine 250mg weekly (after a loading dose of 250mg daily for three days) provided blood samples to confirm compliance and mefloquine concentration (Figure 4). They are assumed to have achieved steady state concentration[132] This sample size was limited by operational contingencies.

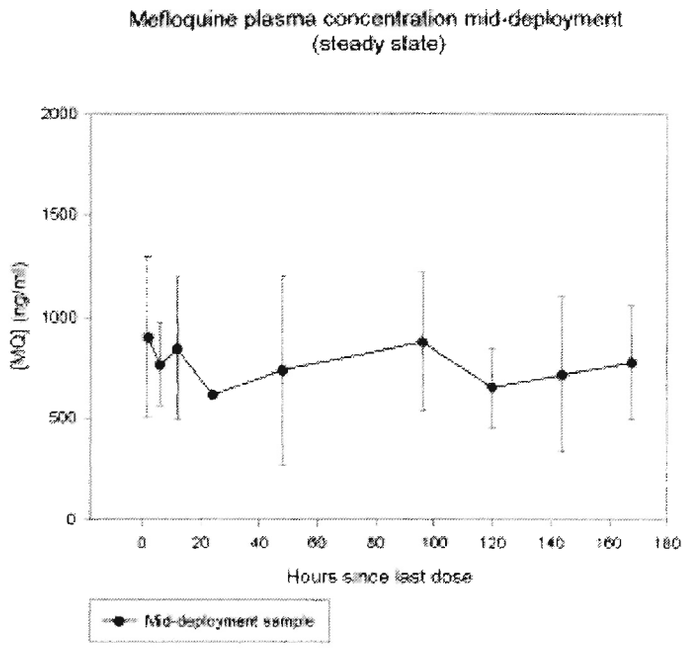

Figure 4: Mean (+/- SD) Mefloquine plasma concentration mid-deployment

Adverse events

The adverse events reported from those volunteers withdrawing from the study are shown in Table 1 (below). Overall, 93 volunteers withdrew from the study before completing the deployment. Of these, 74 (12%) were categorised to be withdrawals due to adverse drug reactions. Sleep disturbances were the most commonly reported reason for withdrawal.

Category	Persons
Admitted to study	652
Consented to participation	642
Started on mefloquine	620 (100%)
Did not complete	93 (15%)
Adverse responses (AR)	74 (12%)
Gastrointestinal AR	9
Mood disturbance	12
Balance disturbance	6
Sensory disturbance	3
Sleep disturbance	24
Other neuropsychiatric	8
Skin manifestations	2
No reason	13

Table 1: Summary of MQ1.6 adverse events and responses
(some volunteers reported more than one reason for withdrawing).

Serious adverse events

Four serious adverse drug reactions were recorded (0.6%) including one seizure experienced by a volunteer with an undisclosed history of a single convulsion. This volunteer was removed from the study. Another volunteer attempted suicide, though this was not attributed to mefloquine after psychological review. He was taken off the study upon evacuation to Australia. There were two episodes of leptospirosis requiring in-patient care. These responded rapidly to doxycycline treatment (200mg daily for 10 days). They were indirectly attributed to mefloquine use, as had the volunteers been using doxycycline chemoprophylaxis for malaria they would not have developed leptospirosis.

Adverse drug reactions

The adverse drug reactions to mefloquine loading dose were investigated immediately using a standard self-administered questionnaire with additional interview should the response warrant. Four hundred and thirteen (67%) questionnaires with complete data were collected after the loading dose (the remainder had incomplete data). A sample of volunteers were again questioned midway through the deployment. The sample was determined by availability within the constraints of the operational circumstances. Two hundred and eighteen questionnaires from the mid-deployment period were matched with post-loading questionnaires.

Nine hundred and thirty eight standardised questionnaires were administered during the repatriation process. These were all self administered and all followed with a medical interview to discuss responses. The sample includes 571 questionnaires and interviews from those volunteers taking mefloquine at that time (including some not originally enrolled in the trial) and 367 from individuals taking doxycycline at that time. This comparison is not considered ideal, however, all respondents served concurrently in the conditions of the same area of operations and were equally able to alter malaria chemoprophylaxis used. Equivalent information was sought by uniform means and effort at this time point. Notwithstanding these aspects, groups were not allocated experimentally; therefore conclusions drawn from this comparison must be made cautiously.

Three reported adverse drug reactions were found to be significantly different between those individuals using doxycycline to those using mefloquine (Table 2).

Adverse reaction	Nil reported		Mild		Moderate		Severe	
Drug[a]	MQ	DX	MQ	DX	MQ	DX	MQ	DX
Sleep disturbance[b]	421 (74%)	296 (81%)	113 (20%)	45 (12%)	35 (6%)	24 (7%)	2 (0.3%)	2 (0.5%)
Headache[c]	513 (90%)	309 (84%)	43 (8%)	46 (13%)	15 (3%)	9 (2%)	0	3 (1%)
Tiredness[d]	486 (85%)	286 (78%)	68 (12%)	67 (18%)	17 (3%)	13 (4%)	0	1 (0.3%)

No significant difference (p>0.05)	Reported events	
	MQ	DX
Anxiety[e]	25 (4%)	19 (5%)
Memory loss[e]	31 (5%)	23 (6%)
Hallucinations[f]	5 (1%)	3 (1%)
Confusion[e]	12 (2%)	12 (3%)
Balance disorder[e]	37 (6%)	27 (7%)
Nausea[e]	93 (16%)	72 (20%)
Vomiting[e]	7 (1%)	7 (2%)
Diarrhoea[e]	40 (7%)	29 (8%)
Abdominal pain[e]	35 (6%)	27 (7%)
Muscle and joint aches[e]	48 (8%)	37 (10%)

Notes:

a. $n_{(Mefloquine)} = 571$;

$n_{(Doxycycline)} = 367$.

b. OR = 1.5; CI: 1.07-2.08; p = 0.01

c. OR = 0.61, CI: 0.41-0.92, p=0.01

d. OR=0.62; CI:0.44-0.89; p=0.006

e. Not significant (1-ß = 0.8)

f. Not significant (1-ß < 0.8)

Table 2: Adverse events reported during repatriation

(following use of doxycycline (DX) or mefloquine (MQ) malaria chemoprophylaxis in East Timor).

Sleep disturbance was more commonly reported in association with mefloquine chemoprophylaxis. Both headache and tiredness were more commonly reported in

association with doxycycline chemoprophylaxis. Detailed collation of these adverse reactions has been included in the table below. Reports of all other adverse reactions for which the questionnaire assayed were not significantly different between the two groups (Table 2). Confidence intervals at the 80% level of power ($1-\beta = 0.8$) exist for all comparisons of reported adverse effects from chemoprophylaxis without significant difference, except for reported hallucinations. Inadequate power to comment on the lack of significant difference between reported hallucinations was probably due to the low incidence of such reports in both groups.

Reported sleep disturbance, headache and tiredness were analysed in detail as they occurred at significantly different rates between the groups using doxycycline or mefloquine chemoprophylaxis at the time of repatriation. This analysis used data derived during the post-loading and mid-deployment questionnaires in an attempt to determine whether adverse reactions particularly associated with mefloquine are predictable. The results of reported sleep disorder, headache and tiredness are tabulated (Tables 3, 4 & 5).

Sleep disturbance

Fifty two percent (217/413) of those questioned following the loading dose of mefloquine reported some degree of sleep disturbance (Table 3).

Sleep disturbance	No problem	Mild	Moderate	Severe	Totals
Post-loading	196 (48%)	131 (32%)	71 (17%)	15 (4%)	413 (100%)
Reported at mid-deployment	81/99[a] (81%)	34/73 (47%)	13/38 (34%)	3/8 (38%)	68/218 (31%)
Mid-deployment reports	150 (69%)	36 (17%)	28 (13%)	4 (2%)	218 (100%)
New report mid-deployment	0	10 (28%)	7 (25%)	1 (25%)	18 (8%)

Table 3: Reported sleep disturbance

(following loading dose regimen for mefloquine and at midway through the deployment)
a. 18 reports of sleep disturbance from 99 individuals questioned who previously did not report sleep disturbance.

The largest proportion of these reports was of mild sleep disturbance only. Mild sleep disturbance is considered that which does not interfere with performance of duties.

Sixty-eight of the 218 volunteers (31%) questioned midway through the deployment reported sleep disorders. Notably, 50 of the 68 reporting sleep disturbance when questioned at this time had originally reported sleep disturbance and were still having the problem. Eighteen percent of volunteers (18/99) now reported sleep disturbance despite not previously reporting the problem. Of these 18 new reports of sleep disturbance midway through the deployment, only eight were moderate or severe,

therefore interfering with performance of duties. Sleep disturbance was apparently a persistent adverse event related to mefloquine chemoprophylaxis in a minority of volunteers.

From the group of soldiers providing a mid-deployment plasma sample (n=203), 30 reported sleep disturbance related to mefloquine. Their various mefloquine concentrations found at this time were plotted against those of the remaining group not reporting sleep disturbance (n=173). There was no apparent difference between the groups (Figure 5).

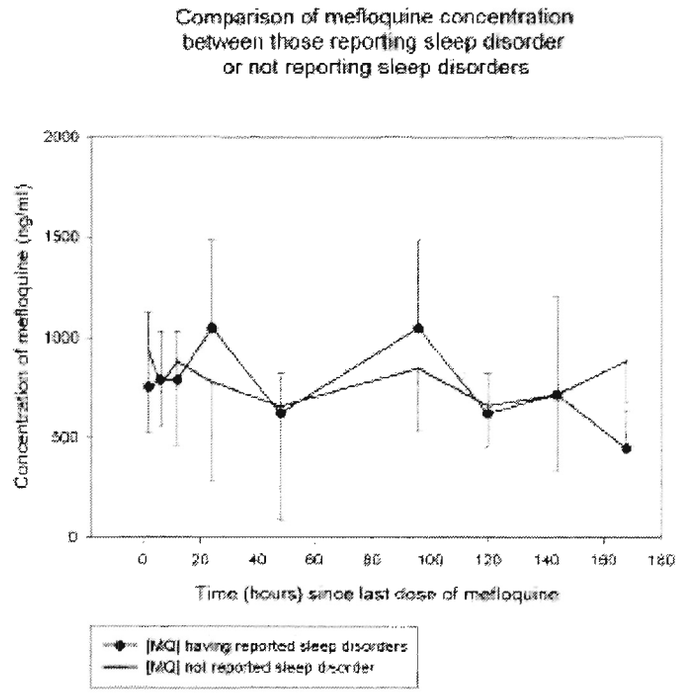

Figure 5: Comparison of plasma mefloquine concentration between those reporting sleep disorder or not reporting sleep disorders

Headache

Thirty percent (123/413) of volunteers questioned reported headache associated with the loading dose of mefloquine (Table 4). Generally, headaches reported at this time were mild (91/124). Only a minority (19/65) of those reporting headache with loading doses was still reporting headache midway through the deployment. Most individuals reporting headache at this time had not previously reported the problem in association with loading doses of mefloquine. Headache was apparently not persistently associated with use of mefloquine chemoprophylaxis.

Headache	No problem	Mild	Moderate	Severe	Total
Post-loading	290 (70%)	91 (22%)	26 (6%)	6 (1%)	413 (100%)
Reported at mid-deployment	133/153[a] (87%)	14/48 (29%)	4/15 (27%)	1 / 2 (50%)	39/218 (18%)

Table 4: Reported headache following loading dose regimen for mefloquine and at midway through the deployment

a. 20 reports of headache from 153 individuals questioned who previously did not report headache.

Tiredness

Forty three percent (176/413) of those questioned following the loading dose of mefloquine reported inordinate tiredness, which they related to starting the drug (Table 5). Most of these reports were of mild tiredness only, suggesting it did not interfere with performance of regular duties.

Tiredness	No problem	Mild	Moderate	Severe	Total
Post-loading	237 (57%)	123 (30%)	47 (11%)	6 (1%)	413 (100%)
Reported at mid-deployment	97/130[a] (75%)	19/63 (14%)	9/24 (38%)	0/1	61/218 (28%)

Table 5: Reported tiredness following loading dose regimen for mefloquine and at midway through the deployment

a. 33 reports of tiredness from 130 individuals questioned who previously did not report tiredness.

Sixty-one of the 218 volunteers (28%) questioned midway through the deployment felt they were experiencing tiredness related to the mefloquine chemoprophylaxis. Few (28/88) reporting tiredness when questioned at this time had originally reported tiredness and were still having the problem. Twenty five percent (33/130) ofthose not previously reporting tiredness had noticed the problem by midway through the deployment. Tiredness was apparently not a persistent adverse event related to mefloquine chemoprophylaxis. Tiredness interfering with performance of duties (moderate and severe reported) was unrelated to sleep disturbance interfering with duties (Table 6).

OR = 13.13; CI: 6.56 – 26.52; p > 0.001	No or mild Sleep disorder reported	Moderate and severe sleep disorder reported
No or mild tiredness reported	310	50
Moderate or severe reported	17	36

Table 6: Reported sleep disturbance related to reported tiredness

Balance disturbance

Reported balance disturbance was analysed in detail to consider the predictability of symptoms reported following a loading dose of mefloquine for subsequent balance problems (Table 7). The overall incidence of reported balance disorders was low. It was as commonly reported following the loading dose (13%) as at mid-deployment (11%). There are very few new cases of balance disturbance reported after loading dose with only nine volunteers reporting the problem of 194 (5%) questioned who previously had not reported this.

Balance disturbance	No problem	Mild	Moderate	Severe	Totals
Post-loading	359	39	13	2	413
Reported at mid-deployment	9[a] (5%)	3 (19%)	1 (14%)	0	13 (6%)
Mid-deployment reports available	194	16	7	1	218
New report mid-deployment		6	3 (1.3%)	0	9[a]

Table 7: Reported balance disturbance following loading dose regimen for mefloquine and at midway through the deployment
a. equivalent cases

Mefloquine and leptospirosis

Two cases of leptospirosis were confirmed and caused hospitalisation during the study period. Both of these cases were soldiers who had volunteered to take mefloquine chemoprophylaxis for malaria. They are considered serious adverse events, as they were hospitalised for a condition that would not have occurred had they been using doxycycline chemoprophylaxis.

Leptospirosis is an acute illness of humans ranging from subclinical infection to a severe and debilitating febrile illness. The severe illness is referred to commonly as Weil's disease, though the disease is also known by many locally applied terms including sugar cane fever, swamp fever and Fort Bragg fever. This has been recognised as a disease of military significance[181,182]

The parasitic and pathological leptospira to humans is *L. interrogans*, a spiral bacteria 6-20μm long and 0.1μm wide. The overall distribution of leptospirosis is worldwide, perhaps the most widespread contemporary zoonosis[183] There are over 200 servars now recognised[184] Each serovar of leptospirosis tends to have a particular geographic distribution, though there is overlap of these distributions.

The main host for leptospirosis is the rat, though many mammals, water birds and some smaller reptiles may carry the bacteria and serve as a source for transmission to humans. Transmission to humans is either by direct or indirect contact with contaminated urine or directly by bites from the carrier animal. Indirect transmission occurs through contact with a fomite contaminated with leptospira, such as soil, mud, water, vegetation, bedding or foodstuffs. In these circumstances contamination arises

from soiling with urine carrying leptospira. Entry to the humans is commonly gained through damaged skin or mucosae. Direct contact may occur from bites or handling of a convalescing or chronic carrying host, typically a rodent. Vector borne transmission is theoretically possible as leptospira have been found in Ixodid ticks and are capable of surviving in mosquitoes and flies for several days, however, the leptospiraemic phase of infection is suitably short to preclude this as a common mode of transmission[183]

Clinical presentations may range from subclinical asymptomatic cases demonstrated only on seroconversion, to severe illness and death. In clinical cases, an incubation period is likely, and while not well defined, is probably less than three weeks. An acute febrile illness with a sore throat, headaches, myalgia and non-specific gastro-intestinal symptoms follow, occasionally with a pre-tibial rash (Fort Bragg serovar). Both cases in this study presented as such (without the rash).

A remission may preceded a second clinical phase in some cases, though in severe primary phase cases, the development of a subsequent phase is imperceptible[185] Neither of the cases in the study had a perceptible remission.

Historically, the diagnosis of leptospirosis employed dark field microscopy of blood or cerebro-spinal fluid samples taken during the acute primary phase of the illness[186] Culture requires special media producing delayed results. Similarly, urine will not carry bacteria until after the bacteraemia is cleared. Physiological parameters may provide support to the diagnosis of a clinical hepatitis usually demonstrating elevated transaminases and alkaline phosphatase. In association with elevated creatine

phosphokinase or polymorphonuclear leucocytosis, some distinction can be made from viral hepatitis. In the presence of haemorrhagic manifestations, bleeding time may be prolonged in the absence of abnormal clotting indices suggesting capillary frailty.

Serological testing is of some assistance in retrospective diagnosis as antibodies begin to rise approximately one week after onset of clinical symptoms and signs. An enzyme linked immunosorbent assay (ELISA) is commonly used, however, other methods include microagglutination may be used for direct investigation of either live or destroyed organisms.

Available in Australia and deployed with the pathology section of ADF Battalion Support Groups in East Timor at the suggestion of AMI has been the Dip-S-Ticks, a field ELISA test kit on blood. This is considered to have adequate diagnostic capability to confirm cases. Both cases tested positive with this test.

The soldiers suffering leptospirosis received 100mg doxycycline twice daily for ten days and recovered completely within this time.

Epileptiform adverse events related to mefloquine

The Australian elements of the operation in East Timor are mounted, or administered by the Headquarters Land Command (LHQ) in Victoria Barracks, Sydney. With the report of a volunteer on the mefloquine study being evacuated from the forward area, the Senior Medical Officer of LHQ requested a report on epilepsy associated with mefloquine. The report submitted to LHQ is attached as Annex I.

Mefloquine psychiatric adverse responses

Attached as Annex J is a report prepared for the Senior Medical Officer of Headquarters Land Command following a suicide attempt by a volunteer on the mefloquine trial in the 4RAR Battalion Group. This case was considered unrelated to the use of mefloquine by the Battalion Group clinical staff.

Chapter 5 - Discussion

Limitations of the study

This study has been undertaken on the basis of opportunity within the operational deployment of Australian Defence personnel into a malarious area. Individuals were required to take malaria chemoprophylaxis in accordance with operational directives which were widened to accommodate the opportunity to use mefloquine and to allow assay of the suitability of this approach. Under these extreme circumstances for clinical research, operational contingencies must remain primary if only to ensure the broader safety of individuals as well as achievement of the peacekeeping mission. Consequently, collection of information has been lacking a certain data points; most evident being the mid-deployment period, though the frenetic activity of the pre-deployment period also prevented data capture. Operational contingencies were certainly not subject to influences by the investigators or external parties with known agenda to influence the outcome of the investigation. These failings are then considered unlikely to have introduced a systematic influence that would bias results other than loss of power and resultant insensitivity.

The logistics of conducting clinical research under operational conditions, the comparison of daily and weekly chemoprophylaxis regimens and the lack of funding, prevented the use of a blinded, randomised trial design to more accurately illustrate the characteristics of these regimens. The design, particularly for the comparison of mefloquine and doxycycline assayed at the close of the deployment, is not optimal, however, has strength in sample size. Conclusions must be drawn from the data derived from the design achieved with cognisance of the assumptions inherent.

Pharmacology

Mefloquine has a long elimination half-life of approximately three weeks[187], though perhaps shorter when used for treatment of acute malaria[188,189] Thus prophylactic use over seven months raises the concern of toxic accumulation[132] The dose chosen for this period was 250mg mefloquine weekly. This dose is considered adequate based on suppressive levels determined in Thailand where mefloquine 360mg fortnightly or 180mg weekly were found to be suppressive of malaria in the north of the country[109] This was extrapolated to 500mg fortnightly for the average 70kg American. The CDC recommended mefloquine 250mg weekly[190,191] rather than fortnightly for chemoprophylaxis based on findings in the Peace Corps studies comparing weekly and fortnightly prophylaxis in western Africa[131] Plasma concentrations achieved by the two regimes were not clearly described, however, 250mg weekly was clearly effective in chemoprophylaxis. The ADF has assumed these recommendations and more recently has begun recording compliance "observed" by immediate military superiors and reported through the chain of command as an operational requirement.

Plasma mefloquine levels achieved at steady state (Figure 4) in the ADF volunteers were consistent with findings at steady state of other military personnel deployed[167] or exercising[122] in tropical regions. The latter group, US soldiers exercising in Thailand enrolled in a double blind controlled trial comparing doxycycline with mefloquine chemoprophylaxis, were found to have comparable adverse events for both drugs and the adverse events were unrelated to plasma mefloquine concentration (for those allocated mefloquine). Dutch Marines deployed to Cambodia generally considered mefloquine to be safe and well tolerated. However, of the small number (14) who

reported adverse effects after one or three months of mefloquine chemoprophylaxis, they had mefloquine concentrations no different to those Marines not reporting adverse effectsi[167]

While it is not specifically mentioned in the scientific literature, the absence of mefloquine activity against leptospira is noted in definitive discussions[184] It is then not surprising to have an outcome of leptospirosis under the circumstances of exposure without concurrent opportune chemoprophylaxis with doxycycline as has occurred in this study. Future consideration of use of mefloquine for malaria chemoprophylaxis must account for the lost benefit of leptospirosis chemoprophylaxis afforded additionally by doxycycline. Conceivably, a similar loss of chemoprophylaxis against other potential organisms sensitive to doxycycline, such as rickettsia, wound infections and gastrointestinal pathogens are opportunity costs of using mefloquine rather than doxycycline chemoprophylaxis for malaria.

Rate of withdrawal

The overall withdrawal rate from mefloquine chemoprophylaxis was 12% over the seven-month period of observation. This is higher than in other military populations using mefloquine chemoprophylaxis under field conditions, though the period of observation and chemoprophylaxis was greater in this study. Only one US Marine of 65 was changed to doxycycline following a loading dose of mefloquine given at sea while deploying to Africa[192,192a] Also, only one of 344 US soldiers deployed to Somalia in 1992/3 withdrew over seven weeks of mefloquine prophylaxis (250mg weekly)[193] Of seventy-three Dutch Marines stationed in Cambodia in 1992, all completed three months mefloquine chemoprophylaxis with no withdrawals[167]

Serving in Mozambique, 1386 Italian soldiers using mefloquine chemoprophylaxis, including 827 with a duration of prophylaxis greater than three months[174], sustained only 0.9% (13 soldiers) withdrawals due to adverse drug reactions.

The high rate of withdrawal in the 4RAR Battalion Group may be due to ready access to medical services and alternate chemoprophylaxis. Also, mefloquine was presented as a "trial drug", while most soldiers were accustomed to using doxycycline for malaria chemoprophylaxis. Volunteers receiving mefloquine were briefed of their unrestricted right to withdraw from mefloquine to use doxycycline. In this process they were requested to identify the reason for withdrawing from mefloquine. While included in the group of adverse drug reactions, 13 volunteers did not give any particular reason for withdrawing. When withdrawing, one volunteer stated he was simply unhappy on the study, another withdrew as he "wasn't comfortable" on mefloquine and others simply removed themselves with no reason given at all. It is possible that presentation to the medical services and withdrawing from mefloquine were symptomatic of the difficult and stressful situation confronting soldiers on forward deployment in armed peacekeeping operations in East Timor.

Sleep disturbance

Mefloquine chemoprophylaxis caused more sleep disturbance among deployed US Marines than chloroquine chemoprophylaxis[157] The effect was more likely during the loading phase of mefloquine; thereafter the reduction in sleep for those using mefloquine averaged only 20 minutes daily. Consistent with our findings, plasma mefloquine concentrations in Marines 72 hours after their last weekly dose were not correlated with sleep or any other adverse effect.

Sleep disturbance was the most common adverse effect of mefloquine chemoprophylaxis for civilian travellers (4%)[152] and Peace Corps volunteers in Africa (9%)[137] The effect was early in the course of mefloquine chemoprophylaxis. The mefloquine metabolite, the racemic levels, the enantiomer ratio and the overall concentration of mefloquine, were all unrelated to reported sleep disturbance[152] Consequently, no causality was attributed, and the association was considered confounded by the effects of travel. For deployment to a peacekeeping operation carrying a significantly higher element of risk than most civilian travel, the psychological influence of the circumstances must be considered in determining causality of sleep disturbance when using mefloquine chemoprophylaxis.

In this study, sleep disturbance was the only adverse event covered in the questionnaire for which a clear association with mefloquine chemoprophylaxis could be demonstrated. Initially, it was of concern that 52% of volunteers questioned following the loading dose reported some degree of sleep disturbance. This is consistent with previous research discussed above. While mild sleep disturbance is that which is noticeable though not interfering with performance of duties, 21% (86/413) of volunteers questioned still indicated sleep disturbance was interfering with the performance of their duties (moderate or severe sleep disturbance). This must be considered of concern in the period prior to deployment. A potential confounding variable is the situation these volunteers find themselves, preparing to leave their families for an extended period of time to deploy to an armed peacekeeping operation. Information on the influence of these circumstances is not readily available. This is a direction for valuable future research.

Sleep disturbance was a persistent problem for 50 of 119 volunteers questioned midway through the deployment whom initially reported the problem following the loading dose. Notwithstanding the possible influence from the confounding situational variables, this is not consistent with other studies in civilian and Peace Corps populations in whom the effect was notable by fading with time. Among US Marines serving in Somalia, a comparable armed peacekeeping operation, sleep disturbance was similar to our findings in being more common at initiation of the loading dose with only partial resolution over time[193]

Eighteen new cases of sleep disturbance were found to arise among the 99 individuals questioned during the deployment having initially not reported any such problem. This is a reasonable percentage of soldiers who may develop a problem in the area of operations without being aware of the problem following loading with mefloquine prior to deployment. Of this group, eight reported sleep disturbance of a nature to interfere with performance of their duties in the area of operations. While the numbers are small, the possibility of approximately eight percent of soldiers developing performance detrimental sleep problems on operation warrants further investigation.

The conclusions drawn are that while sleep disturbance is common with mefloquine chemoprophylaxis and more common than with doxycycline chemoprophylaxis including Australian soldiers deployed on operations, this effect is unlikely to be related to blood concentrations of mefloquine achieved.

Neuropsychiatric effects

In this study, other neuropsychiatric effects were recorded among those withdrawing from mefloquine. The World Health Organisation (WHO) and Hoffman La Roche issued a joint statement and initiated intensive surveillance of all neuropsychiatric events associated with mefloquine in 1989[194] The audit of reported adverse drug responses[135] identified convulsions and neuropsychiatric disturbances including depressive illnesses and psychotic disorders as serious adverse events related to mefloquine. A reporting bias is associated with the use of the term "neuropsychiatric disturbance" without specifying the nature of symptoms fulfilling the criteria for such reporting. Two major neuropsychiatric events (a seizure and an attempted suicide) were recorded in the study group, though other less dramatic neuropsychiatric events were reported commonly by those withdrawing including mood, balance and sensory disturbances.

As with sleep, mood disturbances were more common for US Marines using mefloquine than chloroquine for chemoprophylaxis[157] and the effect typically resolved as tolerance developed. Nevertheless, mood disturbances and neuropsychiatric responses have not been a consistent finding in military populations using mefloquine for malaria chemoprophylaxis. Royal Thai Marines using mefloquine chemoprophylaxis on the Thai-Cambodian border for an extended period of time did not report neuropsychiatric disturbances[134], nor did US peacekeepers in Somalia[193], or Dutch Marines peacekeeping in Cambodia[167] Italian military deployed to Mozambique reported neuropsychiatric adverse reactions with mefloquine, however, they were no more common than in soldiers deployed to Somalia using

chloroquine chemoprophylaxis[174] The British Army exercising in Kenya and operating in Rwanda and Angola have had an incidence of (major) neuropsychiatric reactions no greater than 1:6000 for those soldiers on weekly mefloquine chemoprophylaxis for greater than three months[169] The limited reported Australian military experience previously with this problem has been free of neuropsychiatric reactions[177,180]

Indicators of neuropsychiatric adverse events reported in the questionnaires did not suggest that neuropsychiatric effects were a problem for Australian soldiers above that which would be expected and accepted with the use of doxycycline chemoprophylaxis under operational conditions. Reported anxiety, memory loss and confusion were found not to be significantly more common than experienced with doxycycline chemoprophylaxis. Hallucinations are a potentially more serious adverse event which was reported at a low incidence (<1%) in soldier on both mefloquine and doxycycline. Overall, the incidence of each of these questioned neuropsychiatric symptoms was low.

Balance and sensory disorders have been reported as commonly as sleep disturbance among civilian travellers using mefloquine[152] Such disorders have only occasionally been associated with military populations following the loading dose of mefloquine and is no more common than with chloroquine chemoprophylaxis[157] Peace Corps volunteers also reported dizziness as commonly with mefloquine as chloroquine chemoprophylaxis[135] Balance disruption did not cause any detriment to functional performance among Swiss Air pilots[195] or Israeli military aircrew operating in Rwanda on mefloquine chemoprophylaxis[196]

Despite balance disorder being reported commonly (6% in the mefloquine group), it was not as common as sleep disturbance. The frequency of these reports was also found to be comparable to that with doxycycline chemoprophylaxis (7%). On further investigation, only 1.3% (3/218) of soldiers questioned mid-deployment had developed balance disruptions considered to interfere with their duties. Also, of the 15 soldiers reporting balance disorders upon loading that interfered with preparation for deployment, only one individual noted persistent interference with duties during steady state use of mefloquine mid-deployment.

Balance disorder is not necessarily unacceptable for operational use given sufficient education of soldiers. As balance disruptions associated with doxycycline chemoprophylaxis are accepted for operational purposes, this must also be considered an acceptable level of balance disorder for soldiers on operations using mefloquine chemoprophylaxis. The adverse effect when associated with mefloquine has the benefit of being apparently predictable, usually associated with loading doses of mefloquine, and commonly resolving as tolerance develops. These findings should prompt further investigation into use of mefloquine for military groups such as aviators or divers for which the possibility of balance disruption having a significant adverse influence on duties. For this special group mefloquine is presently contraindicated in favour of doxycycline chemoprophylaxis.

A literature summary of neuropsychiatric events has been tabulated (Table 8).

Paper	Depression reported	Suicides	Total group on MQ
Petersen et al[197]	55	0	809
Barratt et al[148]	143	0	1214
Schlagenhauf et al[152]	33	0	420
Boudreau et al[157]	16	0	157
Totals	247	0	2600

Table 8: Collation of neuropsychiatric adverse events from reported research.

The overall incidence of other neuropsychiatric events with mefloquine chemoprophylaxis may be related to experience and observation bias. In a prospective study for three years the onset of surveillance by WHO and Hoffman La Roche, 28% of recipients of mefloquine treatment in Copenhagen reported one or more neuropsychiatric reactions. Yet in the same duration prior to the WHO reporting requirement, no neuropsychiatric events were recorded in the same medical department[150] Ethical approval of this study required all volunteers to be briefed on all common, uncommon and rare adverse reactions to mefloquine as listed in MIMS Annual 2000. This included neuropsychiatric events that are rare for prophylaxis, though 60 times more common following treatment with mefloquine[89] The appropriateness of this requirement for ethical approval to conduct the study is beyond this discussion, however, it is possible that this increased the reporting of adverse events in the 4RAR Battalion Group personnel.

Gastrointestinal adverse effects

Military personnel using mefloquine chemoprophylaxis commonly report gastrointestinal disturbances, particularly early in the course of taking the drug[157,174] Typically, these are more common with doxycycline than mefloquine chemoprophylaxis[192a,193] However, gastrointestinal symptoms were not commonly the cause of withdrawal from mefloquine chemoprophylaxis in this study nor were they more commonly associated with use of doxycycline chemoprophylaxis. It is possible that the availability of doxycycline at the mess hall has increased compliance in association with food minimising abdominal disturbances.

Chapter 6 - Conclusions

The objectives of the study have been to define the nature of adverse events associated with mefloquine chemoprophylaxis and compare these with those of doxycycline malaria chemoprophylaxis.

Weekly mefloquine malaria chemoprophylaxis does not suit all soldiers under field conditions. Further, mefloquine does not provide opportune chemoprophylaxis against potential concurrent exposures to organisms such as leptospira as does doxycycline. The incidence of withdrawal from weekly mefloquine chemoprophylaxis has been higher in this study of ADF personnel than previously reported among civilian travellers and expatriates as well as military personnel on exercise and operation. This finding may be due to the stress related with this operation for Australian soldiers and the intervention of studying mefloquine chemoprophylaxis under these circumstances.

Sleep disturbance is a relatively common adverse effect with mefloquine chemoprophylaxis. This was confirmed among the Australian soldiers on this operation. While unlikely to be related to the blood concentrations of mefloquine achieved on chemoprophylaxis, sleep disturbance was primarily associated with the loading dose and generally resolved. This disproves one hypothesis tested, that adverse events were equivalent at initiation of chemoprophylaxis as at steady state. The hypothesis is rejected in a manner suggesting "predictability" of mefloquine-related sleep disturbance.

Notably, there were no other adverse effects more commonly associated with mefloquine chemoprophylaxis than that with doxycycline. Findings of comparable adverse gastrointestinal effects, balance disruption and other mild neuropsychiatric events between mefloquine and doxycycline chemoprophylaxis are of clinical interest. That a difference may exist and not been detected due to inadequate power of this study would only support that any such difference in adverse event incidence was small. Tiredness and headache were more common with doxycycline chemoprophylaxis, though on balance the regimen would have to be considered comparably tolerated under these operational conditions.

Further research into the predictable characteristics of soldiers likely to respond badly to mefloquine chemoprophylaxis would be worthwhile for tailored use of mefloquine under operational conditions. Clearly, the pre-existence of sleep disorders, seizures, psychoses or other neuropsychiatric events contraindicate the use of mefloquine chemoprophylaxis.

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Annex A: An outbreak of malaria in a forward battalion on active service in East Timor

(Kitchener SJ, Nasveld PE, Russell B, Elmes N. An outbreak of malaria in a forward battalion in East Timor. *Mil Med.* In press)

Abstract

An outbreak of malaria first developed within 2 RAR, a forward (Australian) Battalion of the International Force in East Timor (INTERFET) in October 1999. Before the Battalion re-deployed to Australia, 17 cases had occurred and in the twelve months following return to Australia, a further 89 cases have occurred, including 18 single recurrences and two second recurrences. The overall attack rate for this deployment of four months, mostly including the wet season of Timor, has been 13.5%. The attack rate for the Battalion (5/7RAR) subsequently occupying this ground (for approximately four months and including the twelve months following redeployment) was 5.2%. Investigation of the initial outbreak and comparisons with the subsequent Battalion suggest major risk factors for contracting malaria were side effects from doxycycline, involvement in night operations, lack of preventive medicine support and the location of platoon positions.

Introduction

The Second Infantry Battalion, Royal Australian Regiment (2RAR) was deployed on active service with the Australian Contingent of the International Force in East Timor (INTERFET) on the border with West Timor. The subsequent Battalion occupying this ground was 5/7RAR, a mechanised infantry battalion deploying for the

conclusion of the wet season from an area of operations closer to Dili. Both Battalions were under operational command of the Third Brigade (3BDE).

An investigation was conducted of an outbreak of malaria in 2RAR that began in October 1999. The battalion has been followed on return to Australia for further malaria cases following eradication. The investigation identifies major and minor risk factors contributing to operational malaria and the overall burden of malaria suffered by the battalion.

Materials and Methods

The initial investigation of the outbreak confirmed diagnosis of all cases to date. The accepted diagnostic criteria for the initial phase of investigation were either thick or thin blood slide or a positive AMRAD ICT test. Identification of parasite was required to be confirmed by the (Australian) Army Laboratory Technicians at the First Forward Surgical Team (1FST) Laboratory or by AMI staff. Bloods slides and AMRAD ICT testing were required to be conducted during the clinical phase of the index condition. Date of diagnosis and date of onset of symptoms were recorded for chronological ordering of cases. Species as determined by these methods were recorded. All samples converted to blood slides were collected and forwarded to AMI, Brisbane, for further confirmation of diagnosis.

All cases manifesting in the first twelve weeks of deployment to East Timor (n=10) were directly interviewed by the Clinical Epidemiologist (CE). All of these cases were in 2RAR. A standard questionnaire used regarding demographics and Service details, onset and nature of symptoms, previous medical history, prior exposure and

activities, personal protective measures, chemoprophylaxis and compliance with these measures, and recollection of vector control and engineering management in locations of activities. From this information, geographic and temporal exposures were confirmed with the records of the Battalion and Company's concerned. A cohort of controls (n=42) were selected from the 3 platoons with the highest attack rate of malaria at the time. All members of this cohort were interviewed by the CE using the standard questionnaire. Company Commanders were interviewed to provide further detail regarding exposures, use of preventative measures and availability of vector control and environmental engineering. Where possible, vector exposure sites were inspected. Direct observation and sampling of breeding sites were employed for larvae samples, man-biting assessments were conducted at sites suspected of transmission, and light traps were used to assess the presence of Anopheline mosquitoes in the evenings. A Scientific Officer (SO) conducted all entomological studies.

Cases developing in Australia following return from East Timor were confirmed with a blood slide returned to AMI with a standard questionnaire (PM40) regarding Service details, demographic information, geographic exposures, episodes of malaria and other diseases while deployed, details of (malaria) prophylaxis used, eradication method and treatment. When necessary uncertain diagnoses were confirmed with PCR at AMI. The Battalion was visited at one and six months after re-deployment to Australia to confirm diagnoses and data.

Results

The malaria cases in 2RAR in East Timor and presenting in the first twelve months after return to Australia are presented in Table 1. Five of the original group of controls subsequently developed malaria, all vivax, including one case in the area of operations, which became multiply recurrent on return to Australia.

There were no deaths associated with this group of malaria cases. All cases were treated at in-patient facilities. The initial seven cases of falciparum malaria were treated at 1FST with Mefloquine 25 mg/kg. Six of these cases were found to have experienced gastro-intestinal or neurological side effects, or both, with this protocol. One case experienced severe neurological side effects. In the latter case, Mefloquine was replaced directly with Proguanil and Atovaquone (Malarone®). The patient resolved symptoms and cleared the parasitaemia over the following 72 hours. For subsequent cases, the conventional protocol for the ADF[1], using Quinine and Doxycycline was adopted. All cases responded to treatments provided. There was no evidence of quinine resistance.

Cases of Vivax malaria in East Timor and in Australia were treated with Chloroquine (600mg followed by 300mg six hours later and 300mg daily on the subsequent two days) followed by Primaquine (7.5mg three times a day for 14 days). All cases, including recurrences responded to Chloroquine. There have been no recrudesces in this group. There have been 18 single recurrent episodes of vivax malaria and two multiply recurrent cases.

On investigation of the first ten cases, all were concluded to have been most likely derived from exposures in and around the Batugade area. The first two cases provided most difficulty in supporting this hypothesis, however, with the assistance of the detailed information of troop movements provided by the Support Company Commander, they were identified to have spent one night in the area 13 days prior to onset of symptoms. In the weeks prior to or following, they had not been exposed to areas found to have Anopheline mosquitoes. Further detail provided indicated they had deployed to the location at short notice to undertake night operations. The initial conclusion drawn was an incubation period for falciparum malaria of 13 days, under these field conditions.

All cases and controls interviewed were using daily doxycycline (100mg) prophylaxis, which had been started prior to deployment to East Timor. One case was not issued doxycycline when admitted for an orthopaedic condition and developed (falciparum) malaria nine days later. Cases could not otherwise be determined to have a different compliance with prophylaxis regimens than controls. Both groups reported difficulty complying with doxycycline when their daily routine was altered such as when patrolling. All cases and 95% of controls reported missing a dose of doxycycline at some time during the deployment. Seventy percent of cases reported gastrointestinal side effects from doxycycline. This was greater than in the control group (40%).

There was an over-representation of involvement in night operations in the group of cases compared to controls, the latter including command and control elements of the Platoons. Both cases and controls reporting night piquet duties indicated they were

not able to use bed nets at this time. All cases and only half of the controls had slept outside the Fort area at Batugade. The area around the Fort was found to have breeding sites and active Anopheline mosquitoes. All cases used a bed net every night (other than when on night piquet duties) at Batugade. Both groups were in the habit of not sleeping in bags when under bed nets and wore short sleeved shirts or short trousers to sleep in at some time during deployment to Batugade. No cases or controls had had the opportunity to treat bed nets (or clothing) since deployment to Timor. Peregin® became available to forward Units after the investigation began.

The one case of malaria that developed in hospital reported to have not used repellent since deploying. All controls and other cases reported to have used repellent during the deployment to Batugade. No individual reported applying repellent before sleeping.

Vector control and environmental engineering activities began in Batugade with the investigation. Health technicians were attached to the Battalion three weeks prior to the onset of the investigation, approximately at the time of the first case, and were supplied with vector control equipment and consumables at the onset of the investigation. No specialised preventive medicine technical control elements were available within the Administrative Support Battalion of the Brigade.

Anopheline mosquitoes were trapped in and around the Fort at Batugade. Breeding sites identified in water bodies around the periphery of the Fort. Local Non-Government Organisation sponsored health services in the location of the internally displaced persons processing point across the river (less than 2km) from the Fort confirmed management of malaria cases in returning refugees and local villagers.

Discussion

The identified major risk factors in this outbreak of falciparum malaria include intolerance of doxycycline, involvement in night operations, the lack of preventive medicine operations to address the vector problem that existed at Batugade, the lack of available chemicals to continue treatment of uniforms and nets, and the location of Platoon sites around the outside the Fort.

The cases investigated in this instance were all initially falciparum malaria. In such an outbreak among Australians, there is a reasonably direct temporal association between exposures and clinical outcomes despite some confounding from prophylaxis. Such conclusions could not have been drawn as readily with vivax cases.

Shanks et al[2] investigated the use of doxycycline by Australian troops under operational conditions in Cambodia and Somalia. Some of the soldiers of this Battalion served in these operations. Doxycycline was found to be satisfactory in these circumstances, though the attack rate was not as high as in the Timor Operation, and the nature of these previous operations are not directly comparable. O'Keefe[3] described malaria in Australian soldiers serving in Vietnam from 1964 to 1972, using Paludrine and later additional Dapsone. The more recent Timor experience indicates that the peak incidence of malaria in 2RAR was not as high as that seen prior to the addition of Dapsone (October 1968) for Paludrine resistant falciparum malaria. Following this, rates in ADF personnel serving in Vietnam after October 1968 were reasonably indicative of that seen in Timor.

Doxycycline is known to be less well tolerated by some individuals[4] On the background of universal incomplete compliance, the intolerance of doxycycline would appear to be the relevant risk factor. It is not possible to exclude the possibility of degeneration of the capsular form of doxycycline carried in blister packs in shirt pockets or personal packs under the operational circumstances. Field durable forms of chemoprophylaxis require more investigation along with weekly chemoprophylaxis regimens, such as mefloquine. Soldiers were generally consuming low residue ration packs, performing at a high physical output in a hot environment potentially reducing bioavailability of doxycycline. This cannot be excluded as a risk factor for malaria and requires further investigation.

Malaria occurring in forward battalions of the ADF serving in Vietnam prior to 1972 was associated with the failure to use bed nets, largely due to conflict with operational contingencies. The identified risk factor of night operations in the 2RAR Timor outbreak is consistent with this conclusion as these operations preclude the use of nets. The ADF distributes four point attachment bed nets; however, suitable attachment points were not readily available in the destroyed buildings and open land around the Batugade fort. These additional operational limitations probably also contributed to compliance.

Notably, the Battalion following 2RAR into this area during the wet season, 5/7RAR, carried an integral, equipped preventive medicine element with a dedicated technical control structure. This formation also reduced residual presence in Batugade and undertook environmental modification to breeding sites in the location. This

Battalion experienced a marked reduction in malaria in and after leaving the area of operations. The outcomes achieved by 5/7RAR support the hypothesis that these were major risk factors.

Conclusions

The ADF experienced a significant outbreak of malaria in forward Battalions during the INTERFET operation. Risk factors identified in investigation include intolerance of doxycycline, involvement in night operations, the lack of preventive medicine technical support, and the location of Platoon sites. Subsequent operations in the area addressing some of these matters demonstrated improved protection against malaria. Further research is necessary into identification of doxycycline intolerant individuals and provision of alternative chemoprophylaxis, the bioavailability and durability of chemoprophylaxis under operational conditions, and field trials of self-standing bed nets.

Table 1: 2RAR Malaria cases presenting in East Timor and in the first twelve months on return to Australia.

	2RAR			5/7RAR		
Onset	ET	AS	Overall	ET	AS	Overall
P falciparum	16	3	19	6	0	6
P vivax	2	65	67	7	23	30
Mixed	1	0	1	1	0	1
Relapses	0	19	19[k]	0	7	7
Totals (episodes)	19	89	108	14	30	44
Attack rate			13.5%			6.3%
Overall rate			41/100py			7/100py

2RAR: Second Battalion, The Royal Australian Regiment

5/7RAR: Fifth/Seventh Battalion, The Royal Australian Regiment

ET: East Timor; AS: Australia

py = person years of exposure

[k] Six are multiple recurrences

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Annex B: Operational malaria in East Timor: six battalions later

(Kitchener SJ, Warwarek P. Operational Malaria in East Timor: six battalions later. *Aust Mil Med.* In press.)

Six battalions have served since the beginning of the International Force in East Timor (InterFET) and transition to the United Nations Transitional Administration in East Timor (UNTAET). Whilst many other ADF Units have also served with InterFET and UNTAET forces, this paper will be limited to discussing the comparison of malaria attacks rates between these six battalion groups to discern factors contributing to mitigation of malaria non-battle casualties.

East Timor

The geography and demography of East Timor relate to the transmission of malaria. The wet season typically arrives in the last quarter of the calender year and continues into the first quarter of the next year. The vector for malaria, the female Anopheles mosquito, steadily increases in number over the wet season due to the increasing

availability of breeding sites. The vector numbers peak several months after the beginning of the season, then transmission follows some months later as increasing numbers of susceptible humans become infected.

The only reservoir for the malaria parasite is a human. Some humans exposed to malaria for much of the year, maintain a degree of immunity, allowing them to tolerate persistence of the parasite in their body without experiencing significant clinical symptoms. These semi-immune carriers of the parasite and people acutely infected and ill with malaria are reservoirs of the parasite.

As the Territory recovers from the infrastructure damage, improved drainage and water storage systems will reduce the number of breeding sites available for the vector. Simultaneously, the recovering health of the population and improved management of malaria cases at health clinics will reduce the size of the parasite reservoir.

The distance of an indigenous population carrying the parasite, from ADF personnel is a risk factor as the flight range of the vector is generally no more than 1.5km. The vector also will not exist or fly higher than approximately 1500m above sea level, nor more than a few metres above ground level.

Initially, populations in the rural areas of East Timor were sparse. As stability improves in the UN territory, internally displaced persons are returning to their homes now in close proximity of several ADF Units. Occasionally, ADF Units have been established adjacent to the path of transient populations.

Protective Measures

Personal protective measures (PPM) include commitment to a 'sleeves down' policy, routinely sleeping under impregnated bed nets, regular application of mosquito repellent to exposed skin and pyrethrin dipping of uniforms and bed nets as well as adherence to anti-malarial medication (chemoprophylaxis). After the outbreak of malaria during InterFET, soldiers were likely to have became more aware of malaria and perhaps more compliant with PPM, however, it is not possible to accurately comment on the comparative compliance with such measures. It is also salient to recognise that several Battalions had conducted exercises in malarious areas prior to deployment to InterFET or UNTAET and sustained malaria non-battle casualties from these exposures.

As well as environmental variables and proximity of malaria parasite reservoirs, battalions have varied in the range and nature of employed protective measures. Preventive Medicine (PM) assets, including personnel, equipment and consumable items were in short supply for the early forward Units in InterFET. Subsequent Units have deployed with larger and more robust integral PM assets under direct command. Later, health and entomological assessment and research teams from the Army Malaria Institute augmented PM assets.

Battalion Analysis

While a comparison of the malaria attack rates of each Battalion serving in East Timor may provide some information regarding prevention and management of malaria, any analysis or comparison of attack rates must be approached cautiously as many environmental, medical and operational variables are involved.

2 RAR

In September 1999, the Second Battalion, RAR, became the first ADF battalion to land in East Timor with InterFET. This Unit remained in the area of operations until mid-January 2000. As the wet season developed, 2RAR deployed out from Dili to part of the area now designated the Australian Battalion area of operations (AUSBATT). This area extends north from the central mountains of the Territory along the border to the Savu Sea. Second Battalion included a resolute though small and lightly equipped PM element, which had difficulty obtaining equipment and supplies. Despite their best efforts, the first ADF malaria case in East Timor occurred in an outbreak striking 2RAR following exposures in the Batugade area.

Plate 1: 2RAR piquet over Batugade Beach, November 1999 – CAPT Bruce Russell identifying Anopheles mosquitoes centre left.

This was a particularly difficult location to hold, with an overwhelming vector problem and an enormous reservoir of parasites available in the transiting internally displaced persons returning from West Timor. The Battalion sustained 19 malaria cases during the four months of deployment in East Timor, an operation attack rate of approximately 3%.

3 RAR

The Third Battalion, 3RAR, deployed shortly after 2RAR into Dili, later onto the border on the Maliana Plain then into the Enclave of East Timor.

The first malaria non-battle casualties from 3RAR were particularly severe with the clinical situation aggravated by the isolation for evacuation. The initial sub-units sustaining these non-battle casualties were experiencing overwhelming exposures to the malaria vector and parasite in the west of the Enclave around Citrana. In late 1999, this area was being rejuvenated both by returning waters into the river delta and returning villagers into the area, providing both vector and parasite. The Battalion headquarters and logistic elements were similarly exposed as the main city of Oecussi, situated on a flat, wet, coastal plain, rapidly increased in population.

Plate 2: Campsite of a 3RAR patrol, Enclave of East Timor, November 1999 – two members of the patrol contracted falciparum malaria within two weeks.

Most of the Battalion redeployed to Australia in February 2000 after five months in the area of operations, having sustained 26 cases, an operation attack rate of approximately of 4%.

5/7 RAR

The Fifth/Seventh Battalion, RAR, maintained security in Dili early in the InterFET operation. The Battalion later extended operations and bases out to Liquicia and others areas around Dili. On a prolonged deployment, 5/7RAR then relieved 2RAR on the northern border in January 2000. The nature and location of operations of this Battalion potentially contributed to the fewer malaria non-battle casualties sustained, however the duration of operations on the northern border areas are comparable to that of 2RAR.

Several significant factors of 5/7RAR mitigated vector borne disease non-battle casualties. The integral mobility of many of the sub-Units of the Battalion allowed withdrawal from hazardous malaria exposure locations during high transmissions periods in the evenings. The Battalion made significant use of heavy engineering support particularly in the Batugade area to reduce vector-breeding sites. The Battalion deployed with a well structured, equipped and supported PM team (1CSST), which undoubtedly benefited 5/7RAR in the prevention of vector borne disease.

Subsequent Battalion Groups have had the advantage of the template provided by 5/7RAR (1CSSB) Group. Despite an extended deployment during a long wet season, the Battalion sustained only 13 malaria non-battle casualties in East Timor, an operation attack rate of less than 2%.

6RAR

With the establishment of UNTAET, 6RAR relieved 5/7RAR in the northern border area. This Battalion was supported by elements from 7BDE including a significant PM team (7CSST). The Battalion also had the benefit of integral mobility and employed engineering support to further reduce malaria vector exposures. Initial assessments of a 'dry season' rotation perhaps reducing malaria exposure were reviewed as rates of malaria from (civilian) health clinics were found to peak after the midyear. Sixth Battalion were likely to have been exposed to the steady rise of parasite burden from increasing transmission occurring after vector breeding sites were established in the wet season and vector numbers increased.

While also using predominantly doxycycline for chemoprophylaxis, 6RAR sustained only seven non-battle casualties from malaria in East Timor, one of which was a reinfection giving an operation attack rate of less than 1%.

1 RAR

The First Battalion, RAR, relieved 6RAR into the second wet season of ADF involvement in East Timor. The Group was similarly equipped with a significant PM team augmented by elements of the Army Malaria Institute performing functions of an health and entomological assessment team aswell as taking a field research role investigating alternative malaria chemoprophylaxis. The 1RAR Battalion Group sustained no malaria non-battle casualties in the area of operations.

4 RAR

The Fourth Battalion (Cdo), RAR, relieved 1 RAR in April 2001. The Group deployed with significant and experienced integral PM assets augmented by health and entomological assessment teams from AMI. The AMI team in collaboration with the medical elements of the Battalion Group also assessed the suitability of weekly malaria chemoprophylaxis using mefloquine (a registered antimalarial agent). Analysis of this assessment will be available shortly. The 4RAR(Cdo) Battalion Group sustained only one malaria non-battle casualty in the area of operations.

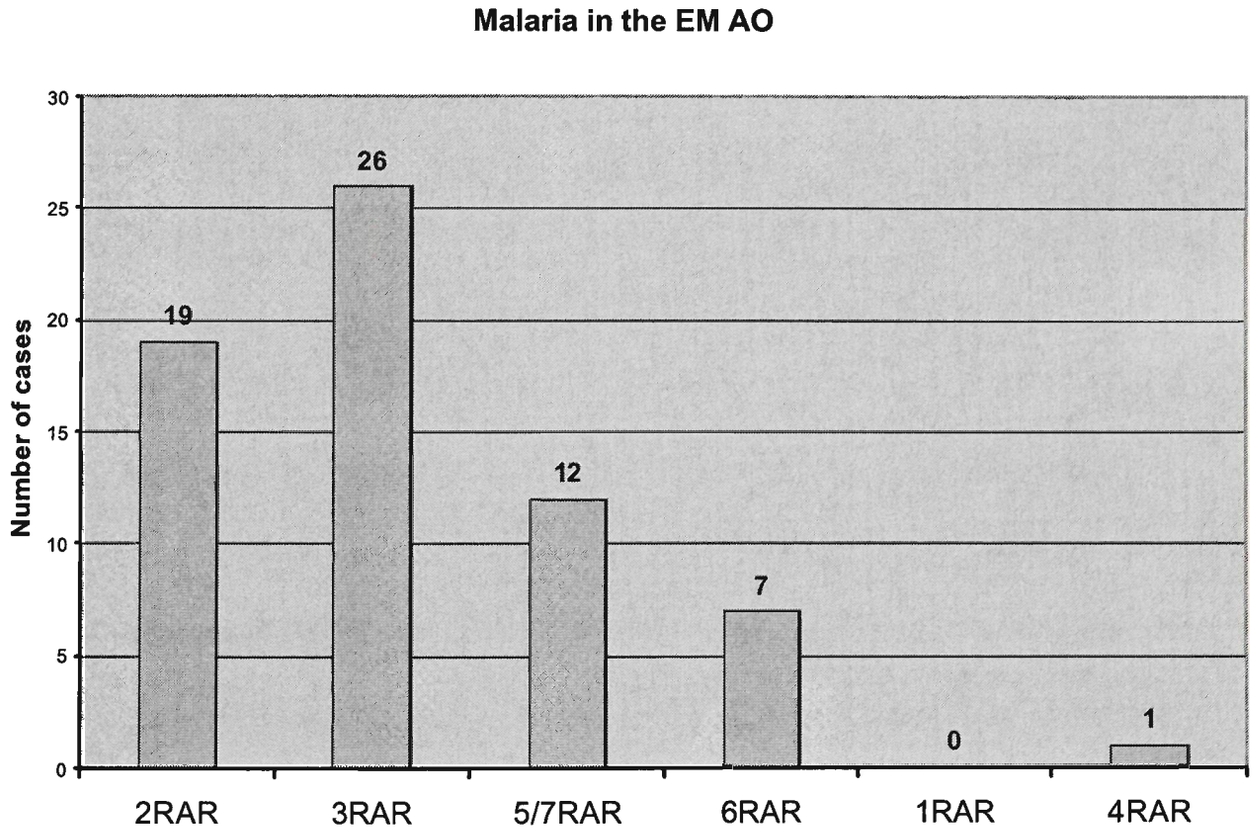

Chart 1: (ADF) Malaria cases presenting in the East Timor area of operations

Discussion

The AMI deployment to East Timor began with investigation of the malaria outbreak during InterFET. Since the outbreak, investigations have concentrated on recording the impact of malaria, antimalarial chemoprophylaxis, identifying and mapping the vector in the field, testing the acceptability of bed nets and repellents, and charting resistance to antimalarial drugs among the local malaria parasites. The vector for malaria is widely present in the AUSBATT and the local populations are effected by malaria seasonally, though to some extent all year. There is no evidence of resistance to doxycycline in East Timor, though the effectiveness of doxycycline was questioned[1] This is consistent with the experience on other military operations[2] Other military forces have found weekly malaria chemoprophylaxis regimens more suitable for operations[3,4] and exercises in malarious areas[5] and may have been the case during InterFET for those peacekeeping forces using weekly mefloquine[6]

Initially, the operational attack rates for 2RAR and 3RAR were comparable to that recorded for Australian Forces in Vietnam prior to the introduction of effective malaria chemoprophylaxis with Dapsone in 1968[7] The subsequently developing pattern in preventative management of malaria at the Battalion level is quite evident with the evidence now available (Table 1). The distinct reduction in operational malaria with the deployment of PM assets integral to 5/7RAR sustained with 6RAR supports the value of these assets when well equipped, supported and commanded.

As East Timor re-establishes infrastructure, a reduction in breeding sites for vectors and the human carriage of malaria parasites will reduce the malaria risk. Notwithstanding this potential reduction in malaria exposure and that 4RAR Battalion

Group carried comparable PM assets to that of the 6RAR Group, however, sustained only one malaria non-battle casualty during a deployment in similar seasons and the 1RAR Group deployed with no malaria casualties. The apparent additional factors of weekly malaria chemoprophylaxis and the presence of an health and entomological assessment team augmenting PM assets has allowed the ADF to deploy a sizeable unit of professional educated soldiers into a highly malarious area on hazardous operations sustaining minimal non-battle casualty from malaria.

Conclusion

Progressively, the integration of PM elements and health and entomological assessment teams has apparently reduced non-battle casualties sustained from malaria. Tailoring malaria chemoprophylaxis has contributed. The next challenge is prevention of post-deployment malaria non-battle casualties through further tailoring of antimalarial agents for operations.

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Annex C: Self treated relapsing vivax malaria?

(Kitchener SJ, Ashford B. Self treated relapsing vivax malaria? *Aust Mil Med.* In press)

This is a report of a case of malaria in which the patient may have partially treated an undiagnosed episode of malaria before presenting with what would then be a relapse of the initial episode. It is presented for discussion with military health professionals who may see such cases.

The patient is a male, 80kg infantryman who had an unremarkable medical history (ADF Medical Class 1). He began mefloquine chemoprophylaxis, reporting no adverse effects following the loading dose, prior to deploying into East Timor.

Within two weeks of arriving in the area of operations he presented with headache, initial insomnia and early waking, muscle and joint aches, which he did not feel impaired the performance of his duties. His sleep disturbance typically followed picquet duty. He ceased mefloquine chemoprophylaxis and began doxycycline 100mg daily.

Three months after transferring to doxycycline, he presented with arthralgia, fevers and chills, sweats, sore throat and a productive cough with yellow sputum. He was noted to have sublingual lymphadenopathy and pharyngitis, which was treated with Betadine gargle. At this time, having spoken with a friend who had leptospirosis, he began self-treating (undisclosed) with doxycycline 100mg twice daily. After some

improvement the following day, he developed peripheral paraesthesia, loss of appetite, myalgia and increasing tiredness by the third day. No malaria parasites were seen on thick and thin blood films. He was treated with chest percussion and oxygen delivered by mask. By the eighth day, symptoms had resolved and he returned to doxycycline 100mg daily.

Six weeks after the onset of the previous episode, he developed nausea, fever, chills, myalgia and began double dosing with doxycycline again. Symptoms abated the following day, however returned on the third day when he represented febrile (39^0C), alert and orientated though sweating profusely and complaining of headache, cough and shortness of breath. At this time, he was noted to have no clinical abnormality of the neurological or respiratory systems and no hepatosplenomegaly. Intravenous fluid and simple analgesia were begun as the patient was turned into the Battalion Support Group Regimental Aid Post.

Plasmodium vivax trophozoites and gametocytes (680/uL) were identified on blood slides. Treatment with Chloroquine 1500mg over the next three days produced rapid recovery and he moved to Dili for repatriation and further management by AMI clinicians.

Discussion

The patient deployed on mefloquine chemoprophylaxis though ceased this shortly after entering East Timor. His sudden withdrawal despite a symptomless loading dose suggests the symptoms were at least contributed to by the circumstances of deployment. His first clinical episode occurred well after conclusion of mefloquine chemoprophylaxis, as such is unlikely to be related.

The febrile periodicity (second daily) of the earlier clinical episode is consistent with vivax malaria and the same as that observed subsequently. The symptomatology is also similar with the second episode and consistent with vivax malaria. This supports the hypothesis that he has suffered two episodes of vivax malaria, the first being only partially treated.

Doxycycline is generally effective in ***suppression*** of vivax malaria for Australian soldiers[1] If the earlier clinical episode reported in September was related to a *P. vivax* infection, this would imply a failure of doxycycline chemosuppression. In favour of this is that the patient normally took doxycycline with breakfast, however, recalls missing two tablets only when on patrol two weeks prior to the first clinical episode. The incubation period for vivax malaria is approximately two weeks.

The soldier has used double dose of doxycycline for eight days during the acute phase of a condition consistent with malaria. Doxycycline treats malaria, including vivax malaria, slowly and by only addressing the blood stages leaving residual hepatic stages (hypnozoites) unaffected[2]. The overall efficacy and possible time to reappearance of parasites from failure of such a treatment with doxycycline is difficult

to determine. Treatment with quinine and doxycycline (100mg twice daily for seven days) can allow reappearance of parasitaemia as early as two weeks after starting treatment[3] due to their short half-lives suggesting failure to clear all parasites, compliance or absorption problems, or false (original) positive blood smears[4]

While doxycycline cannot be relied upon for causal prophylaxis (removal of liver and blood stages of *P. vivax*), the release of blood stage merozoites is generally well suppressed by doxycycline[5], therefore, at some stage this patient has transiently allowed establishment of infection. It is possible that the first clinical episode is true vivax malaria only partially treated with double dose doxycycline, suppressing parasitaemia below detectable levels, then gradually re-establishing to another clinical episode.

As the possibility exists that the confirmed episode was a relapse of vivax malaria, the patient was also treated with 6mg/kg primaquine given as 30mg daily with food for 16 days. He tolerated this treatment well. Three months later, he has not developed further parasitaemia.

Conclusion

The only recalled non-compliance with doxycycline is the most likely time for instigation of infection. Self-treatment with doxycycline 200mg daily only slowly manages *P. vivax* parasitaemia; however, doxycycline 100mg daily may be less likely to maintain chemosuppression of an established (albeit low grade) parasitaemia.

Overall, this case demonstrates the requirement for vigilant prophylaxis. It also re-enforces the value of history in the clinical diagnosis of malaria. This should encourage generalist Medical Officers to undertake initial management of malaria with confidence.

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Annex D

Members of the Australian Defence Health Research Committee are:

Air Vice Marshall Bruce Short FRACP, Surgeon General of the Australian Defence Force (Chairman)
Major General John Pearn AM RFD FRACP

Colonel Peter Warfe CSC FAFPHM

Justice Terence Higgins

Reverend Monsignor Max Davis AM RANR

Dr. Alan Twomey PhD

Mr. David Dillon

Mrs. Elizabeth Grant

Following are:

ADMEC Minute DHSB 320/2001 – provisional approval for the study

ADMEC Minute DHSB 1127/2001 – acceptance of amendments

DEFENCE PERSONNEL EXECUTIVE
DEFENCE HEALTH SERVICE BRANCH

CP2-7-66 Department of Defence CANBERRA ACT 2600

2001/5344
ADMEC 249/01
DHSB 320/2001

Major S. Kitchener
Officer In Charge Clinical Trials
Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Major Kitchener,

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) PROTOCOL 249/01: EVALUATION OF MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS

1. ADMEC has considered your protocol and approves in principle. However, some amendments are required before formal ethical clearance is given.
2. In particular ADMEC agreed to accept the protocol on the following conditions:
    a. The information and consent sheet are to be amended to clearly outline in quantitative terms the side effects of the medication, including CNS and cardiovascular side effects, and are to include rare events as well as common.
    b. The study should be retitled "Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers"" to more accurately reflect the intent of the study, and

c. Six doses of the medication are to be given in Australia prior to deployment.

3. Please note that this protocol will be considered to be "pending" until the required amendments are received and sighted by the Executive Secretary. If all requirements have been met, your project will be formally approved and a Researcher's Agreement forwarded for your signature.
4. Please contact me if I can be of any assistance.

Yours sincerely,

M. BLENKIN
Lieutenant Commander
Executive Secretary
Australian Defence Medical Ethics Committee

Tel (02) 62663818 Fax (02) 62664982

Intentionally blank

DEFENCE PERSONNEL EXECUTIVE
DEFENCE HEALTH SERVICE BRANCH

CP2-7-66 Department of Defence CANBERRA ACT 2600

2001/5344
ADHREC 249/01
DHSB 1127/2001

Major S. Kitchener
Officer In Charge Clinical Trials
Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Major Kitchener

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADMEC) PROTOCOL 249/01: EVALUATION OF MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS

1. Thankyou for submitting for protocol modification version 1.5 dated 5 June 2001. The proposed amendments were considered by The Australian Defence Human Research Ethics Committee on Monday the 18th of June 2001.
2. ADHREC has considered your protocol and has approved the amendment. As such the protocol is now cleared to proceed with these modifications in place.
3. Please contact me if you would like to discuss this further.

Yours sincerely,

R.A. LANDY
Major
Executive Secretary
Australian Defence Human Research Ethics Committee

Tel (02) 62663807 Fax (02) 62664982
02 July 2001

Annex E: Consent Form Protocol

Regimental Number: _____ Volunteers Initials: _____
You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY.
As you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to observe a less commonly used drug, Mefloquine, under field conditions.
The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent malaria infection from overseas deployments in the future.

WHAT IS THE MEDICINE?
Mefloquine one tablet weekly in the AO and for two weeks after return to Australia. You will initially be given at least six tablets prior to deployment. The usual medicine is Doxycycline one tablet daily through deployment and for two weeks after. You are initially given two tablets prior to deployment.

WHAT IS THE STUDY?
The study is looking at how satisfactory Mefloquine is under field conditions. You will be provided with one tablet weekly through the standard supply system in the field. Supply and use of each tablet weekly will be recorded. You will be asked immediately prior to deployment, several times throughout the deployment and on return to Australia, whether you had any problems you thought were due to the antimalarial tablet. A small group will be (randomly) selected to additionally give blood on two occasions during deployment.

LENGTH OF THE STUDY
The study will begin 4 weeks prior to your redeployment and will be continued until 12 months after your deployment is completed. Your only involvement after redeployment will be if you develop malaria.

STUDY TESTS
All volunteers will be asked to complete a questionnaire immediately prior to deployment, during deployment and prior to returning to Australia. As the investigators are looking at baseline drug levels in blood, and measuring biochemistry and haematology levels to monitor safety, a small group will be requested to donate two samples of blood from your arm. The amount of blood collected for the study amounts to no more than about 20mls, or the equivalent of 4 teaspoons.

RISKS / DISCOMFORTS
There may be some bruising with blood taken from the veins in your arm.

When Mefloquine is used to treat people ill with malaria especially children less than 45kg, side effects have been reported and recorded. These include over 1% reporting sleepiness, insomnia, abnormal dreams, dizziness, loss of balance, headache, nausea and vomiting, diarrhoea or abdominal pain. Less than 1% had episodes of anxiety, confusion, depression, restlessness, forgetfulness, hallucinations and psychotic or paranoid reactions, nerve damage, convulsions, tiredness, fever, chills, loss of appetite, rash, itchiness, hair loss, visual disturbances, muscle weakness, cramps, muscle and joint pain, ringing in the ears, hearing disorders, low or high blood pressure, fainting, palpitations, extra heart beats, slow heart rate, or lowering of the clotting cells in the blood, or white cells (used for fighting infection) and fewer than 0.1% had brain damage, psychotic events, severe hypersensitivity reactions in the skin and heart block.

Overall, Mefloquine has fewer side effects than Doxycycline in trials among travellers (including Australians).

PRECAUTIONS
If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have had any anxiety attacks or serious depression in the past you also may not be able to use Mefloquine. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

CONFIDENTIALITY
In all reports only a number will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION
Mefloquine is authorised to use as an antimalarial by civilian authorities in Australia in addition to being directed for use as an alternative to Doxycycline by the Director General, Defence Health Services in HPD215. This trial has also been approved by the Australian Defence Medical Ethics Committee.
All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the RMO or AMI (0407 150384).

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the RMO or study investigators. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP2-7-66
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3925

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal antimalarial course of Doxycycline daily and an eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.
I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____ **Date:**_____

INVESTIGATOR'S SIGNATURE _____ **Date:**_____

Annex F: Adverse experience guidelines

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out below.

Eliciting and Documenting Adverse Experiences

It is the responsibility of the investigator to document all adverse experiences which occur during the investigation. An adverse experience includes any noxious, pathological or unintended change in anatomical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical study whether associated with the study drug or placebo and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the case record under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences.

In the case of studies involving a marketed drug in an established indication, an adverse experience includes significant failure of the expected pharmacological or biological action.

All adverse experiences occurring after the start of the study must be reported. Subject entry into the study is defined as the time at which informed consent is obtained (This must be before any protocol-specific diagnostic procedures or interventions) All subsequent adverse experiences, whether no drug (ie. during reference 'run-in' or 'wash-out' period) or when active drug or placebo is being administered, must be reported REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.

At each visit /assessment, adverse experiences will.be evaluated by the investigator. Adverse experiences not previously documented in the study will be recorded in the adverse experience section of the subject's case record form. The nature of each experience date and time (where appropriate) of onset, duration, severity and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the case record form.

Adverse experiences already documented in the CRF ie. at a previous assessment and designated as 'continuing' should be reviewed. If these have resolved, the documentation in the CRF should be completed. NB. If an adverse experience changes in frequency or severity during a study period, a new record of the experience will be started.

Ask the subject or the subjects parent or legal guardian a non-leading question such as:
"Do you feel different in any way since starting the new treatment/the last assessment?"

Assessment of Severity

Maximum intensity should be assigned to one of the following categories:

Mild: For example, an adverse experience which is easily tolerated by the subject, causing minimal discomfort not interfering with everyday activities.

Moderate: For example, an adverse experience that is sufficiently discomforting to interfere with normal everyday activities.

Severe: For example, an adverse experience which prevents normal everyday activities

Assessment of Causality

Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: ***not related***, ***unlikely***, ***suspected*** (reasonable possibility), ***probable.***

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, eg. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

Known pharmacology of the drug

Reaction of similar nature being previously observed with this drug or class of drug

The experience having often been reported in literature for similar drug as drug related eg. skin rashes, blood dyscrasia

The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

Following-up of Adverse Experiences

Investigators should follow-up subjects with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the subject's subsequent course must be submitted to the clinical study monitor.

Serious Adverse Experiences

Definition of Serious Adverse Experiences

A serious adverse experience is any event which is fatal, life threatening, disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event.

Life threatening – definition:

An adverse experience is life threatening if the subject was at immediate risk of death from the event as it occurred; ie. It does not include a reaction that if it had occurred in a more serious form might have caused death For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Disability /incapacitating definition:

An adverse experience is incapacitating or disabling if the experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions

Reporting Serious Adverse Experiences

Any serious adverse experiences that occur during the clinical study whether or not related to the study drug, must be reported by the investigator to the study monitor (by telephone within 24hrs).

All serious adverse experiences must be reported by telephone within 24hrs to the study monitor or Principal Investigator.

Name: Major Scott Kitchener

Telephone: 0407 150384

The telephone report should be followed by full written summary detailing relevant aspects of the adverse experiences in question. Where applicable information from relevant hospital case records and autopsy reports should be obtained.

Instances of death cancer or congenital abnormality if brought to the attention of the investigator *AT ANY TIME* after the cessation of study medication and linked by the investigator to a previous clinical trial, should be reported to the study monitor.

Overdose

Any instance of overdose (suspected or confirmed) must be communicated the Principal Investigator within 24 hours and be fully documented as a serious adverse experience. Details of any signs of symptoms and their management should be recorded including details of any antidotes administered.

Pregnancy

Subjects who become pregnant during the dosing periods (clearing dosing and prophylactic dosing) should discontinue dosing immediately. However subjects who become pregnant during the followup phase of the study should continued to be monitored as originally scheduled.

Subjects should be instructed to notify the investigator if it is determined after the completion of the study that they became pregnant either during the treatment or prophylaxis-dosing phase of the study or during the followup period.

Whenever possible a pregnancy should be followed up to term, any premature terminations reported, and the status of the mother and child should be reported after delivery.

Annex G: Adverse event record form

Name:_____ Regimental Number _____

Date of presentation: / /
Following Loading dose ☐ (tick one)
Field Evaluation ☐
RTA ☐

MQ001

Record reported adverse events as:

1. Mild (present but didn't impair completion of duties)
2. Moderate (some impairment of duties), or
3. Severe (prevent completion of duties

All reported symptoms must be rated: 1. 2. OR 3.

Return form with PM105 to RMO 4RAR

Symptoms	Rating	Comment
Nausea		
Vomiting		
Diarrhoea		
Abdominal pain		
Headache		
Tiredness		
Anxiety		
Confusion		
Memory Loss		
Hallucinations		
Sleep problems		
Muscle aches		
Joint aches		
Balance problems		
Skin Reaction		
Hearing Problems		
Comment on activity status		

Record all clinical history on PM105

PI contacted Yes / No
Bloods Taken Yes / No – Comment _____

Annex H

Summary of Protocol

TITLE	Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers
SPONSOR	Australian Army Malaria Institute
PLANNED STUDY START	April 2001
INDICATION	Malaria prophylaxis
INVESTIGATOR	Major Scott Kitchener – Australian Army Malaria Institute
OBJECTIVES	The objective of the study is primarily to define the safety and tolerability of mefloquine under operational conditions. Secondary objectives are to assess the effectiveness of mefloquine under operational conditions.
STUDY DESIGN	Active reporting of adverse events / side effects to medication using a questionnaire system, pharmacokinetics (on a core group of one Company), log returns for compliance review and active surveillance for malaria cases.
SAMPLE SIZE	800 volunteers.
SELECTION CRITERIA	Volunteers recruited from exposed groups of troops serving in East Timor (4RAR and 2RAR Battalion group core elements).
FORMULATIONS	1. Mefloquine 250mg, third daily for 3 doses, then weekly, 2. Primaquine 15mg bd for 14 days on RTA. 3. All volunteers on primaquine continue with mefloquine weekly as per current ADF policy
ROUTE OF ADMINISTRATION	Oral
OUTCOME VARIABLES: **SAFETY AND TOLERABILITY** **EFFECTIVENESS**	 Clinical adverse events Changes of laboratory values (haematology, biochemistry, plasma drug levels Compliance Protection from malaria infections

Overview of Study - Protocol No: MQ001

	Screening	Loading Safety	Field Safety	Followup[1]
Study Visit	1	2	3	As required
Day (D)	Prior to deployment D-25 (days)	D-7	Variable	As required
Written informed consent	*			
Inclusion/exclusion Criteria	*			
Physical Examination				*
Medical history/ Demography	*		*	*
Medication issued	*			Supply by RAP in field conditions
Malaria blood smears				*
Haematology/ Biochemistry		*		*
Pharmacology		*	*	*
Pregnancy test	*			* (if female)
Adverse event review		*	*	*
Concomitant medicine review	*	*	*	*

Notes:

1. Follow-up initiated by treating medical facility in cooperation with AMI Investigators once diagnosis of malaria has been made.

Annex I: Epileptiform adverse events related to mefloquine

Four months after loading doses of mefloquine were administered and prophylaxis established, and approximately fourteen weeks after arriving in the area of operations the male officer developed a generalised epileptic seizure during a patrol. Non-medical personnel witnessed the seizure. He was moved by tactical air evacuation to the United Nations Military Hospital in Dili for immediate high level care. On arrival he was post-ictal. Supportive care was initiated. Strategic evacuation followed one day later when the patient was considered stable by the attending phyician.

The patient reported two previously undisclosed seizures in the years prior to service in East Timor. These were not investigated and no treatment had been received initially or for prevention.

Concurrent factors potentially predisposing to the development of a seizure include the history of previous episodes in addition to several environmental factors. Immediate and preceding environmental factors include dehydration of the individual associated with the hot environment, humidity and his level of physical exertion. His physical condition has potentially been compromised associated with over three months active service in the forward areas of East Timor. At the time of the seizure the patient may not have eaten for in excess of 12 hours prior, however, there is no evidence of glucose intolerance, he was not diabetic prior to beginning the prophylaxis, nor was he using any diabetogenic medications prior to onset of the seizure.

Mefloquine has been related to neuropsychiatric adverse events of which seizures are a large proportion[1] A series of serious neurological and psychiatric adverse reactions to mefloquine, convulsions were reported more commonly than depression[2] From early case reports following registration known controlled epileptic patients have developed seizures shortly after onset of prophylactic doses of melfoquine[3,4] Seizures have been observed in those not previously known to be epileptic[5] Individual case reports have arisen in Australians and the considered recommendation is that mefloquine should not be prescribed for malaria chemoprophylaxis for those travellers with known history of epilepsy[6]. Seizures are highly likely to have been chemically induced[7], as is known to be the case with other quinine derived antimalarial agents[8]

In a small series[9] of epileptic adverse events following the use of mefloquine for malaria chemoprophylaxis, the majority (5/6) of individuals were noted to have no history of epilepsy. The single patient reporting previous epilepsy had not experienced a seizure for more than five years prior. All adverse events in this series presented within the first three weeks after onset of chemoprophylaxis.

Notably, most of the reported episodes are observed in individuals receiving chemoprophylaxis doses suggesting sensitivity innate to the chemical exposure rather than an effect of accumulated dose. Notwithstanding this, there is the potential for epilepsy in the presence of complicated malaria and the doses of mefloquine used for treatment are much greater than those for chemoprophylaxis. There are no reports of epilepsy or other seizures developing after a prolonged period on chemoprophylaxis with mefloquine.

Appropriate clinical management in preparation for travel using mefloquine chemoprophylaxis is to construct a risk ratio with the traveller prior to departure regarding the balance of malaria exposure and known serious adverse events[10] Those travellers known to have a history of epilepsy should be recommended not to receive mefloquine nor chloroquine chemoprophylaxis.

The more difficult group to determine the risk of epileptic adverse events are those without a history of epilepsy whether or not they have other potential risk factors such as a family history or history of infant febrile convulsions. It is apparent that the occurrence of epilepsy as an adverse event related to the use of mefloquine will be early in the course of exposure to the agent. While this has potentially disastrous effects on the management of a seriously ill patient treated with mefloquine for complicated or potentially resistant malaria, the predictability of early adverse event development provides a benefit for the traveller using mefloquine for malaria chemoprophylaxis. This would suggest that in any traveller for whom a potential risk of developing epilepsy has been identified on pre-travel history, a loading dose or trial dose equivalent to loading dosage well prior to travel may provide some evidence to lower concern of epilepsy once travel has begun.

References:

1. Weinke T, Trautmann M, Held T, Johnson R, Letz R, Tschopp A, Vranjes N, Bergquist Y, Ericsoson O, Hellgren U, Rombo L, Mannino S, Handschin J, Sturchler D. Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg* 1991;**45**(1):86-91.

2. Bem JL, Kerr L, Stuerchler D. Mefloquine prophylaxis: an overview of spontaneous reports of severe psychiatric reactions and convulsions. *J Trop Med Hyg* 1992;**95**(3):167-79.

3. Besser R, Kramer G. [Suspected convulsive side-effect of mefloquine (Lariam)]. *Nervenarzt* 1991;**62**(12):760-1.

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7. Singh K, Shanks GD, Wilde H. Seizures after mefloquine. *Ann Intern Med* 1991;**114**(11):994.

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10. Durrheim DN, Gammon S, Waner S, Braack LE. Antimalarial prophylaxis--use and adverse events in visitors to the Kruger National Park. *S Afr Med J* 1999;**89**(2):170-5.

Annex J: Mefloquine psychiatric adverse responses

The tolerability of mefloquine has been reviewed against doxycycline, chloroquine and the combination of chloroquine and proguanil in several studies. Though compliance with mefloquine is better and the rate of overall side effects is no different between the regimens[1,2,3,4], neuropsychiatric reactions specifically are more common with mefloquine use for malaria prophylaxis[5]

The first scientific literature regarding significant psychiatric side effects associated with mefloquine was in 1990 with the anecdotal report of a female with previous psychiatric history who attempted suicide by drowning after her second tablet[6] Other than an antecedent psychiatric history the patient had also experienced an acute psychiatric episode that lasted five days after her first tablet, yet continued to the second dose. In 1991, 12 cases of neuropsychiatric adverse events following mefloquine therapeutic and prophylactic use in Africa were investigated. Cases mainly consisted of seizures, acute psychoses, anxiety neuroses and sleep disturbances and notably occurred early after exposure to mefloquine[7] Seven years after registration of mefloquine (1992), 59 serious neurological and psychiatric reactions to mefloquine had been reported worldwide[8] including acute depression following treatment level doses of mefloquine[9]

Direct comparison of mefloquine and doxycycline in military personnel suggested they were equally well tolerated in the field[10,11,12] including on active operational service[13] Nevertheless, mefloquine has been noted to be related to insomnia and depressive illness in (US) military personnel, the effect on depression particularly was

noted to occur early in the course of taking prophylaxis then resolved[14] Similarly, in Dutch travellers using mefloquine, proguanil or nothing for malaria prophylaxis, despite the relative risk of insomnia being 1.6 in the mefloquine group, the excess risk was 6% and depression was no more common[15] Nevertheless, another Dutch civilian study found the excess risk of depression in travellers to be 7.2% over those travellers using proguanil for prophylaxis[16] Depression was found to be more common among civilian travellers to Kruger National Park using mefloquine for malaria prophylaxis compared to those travellers using chloroquine with proguanil[17] It was also more commonly reported by Danish travellers using mefloquine for prophylaxis compared to those using chloroquine or chloroquine and proguanil[18]

In summary, neuropsychiatric adverse events occur following use of mefloquine. These are more common following therapeutic use (1/215) than use for prophylaxis (1/13000)[19] Insomnia is more likely with the use of mefloquine for malaria chemoprophylaxis by military personnel. Depression is also more likely with use of mefloquine than proguanil, chloroquine or the two combined for malaria prophylaxis. The depression associated appears to be a transient effect with non-fatal outcomes and resolution or tolerance early in use of mefloquine. Suicide has only been found to follow florid acute psychotic episodes.

In collating some of the literature identifying travellers who have used mefloquine and developed depression or other neuropsychiatric disease, several hundred are reported from several thousand travellers, however, no cases of suicide resulted.

Paper	Depression reported	Suicides	Total group on MQ
Petersen et al[20]	55	0	809
Barratt et al[21]	143	0	1214
Schlagenhauf et al[22]	33	0	420
Boudreau et al[23]	16	0	157
Totals	247	0	2600

Collation of neuropsychiatric adverse events from reported research.

References:

1. Huzly D, Schonfeld C, Beuerle W, Bienzle U. Malaria Chemoprophylaxis in German Tourists: A Prospective Study on Compliance and Adverse Reactions. *J Travel Med* 1996;**3**(3):148-155.

2. Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC. Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993;**341**(8849):848-51.

3. Steffen R, Fuchs E, Schildknecht J, Weber G, Eichenlaub D, Fleisher K, Kern W, Pohle HD. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa. *Lancet* 1993;**341**(8856):1299-303.

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11. Conrad KA, Kiser WR. Doxycycline vs. mefloquine. *Mil Med* 1997;**162**(1):viii.

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