

The military experience of mefloquine malaria chemoprophylaxis

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MEFLOQUINE DISCOVERY and development have been intimately associated with military imperatives, contingencies and requirements. This article discusses military experience with mefloquine in an attempt to generate a perspective for future policy.

The development of mefloquine as an antimalarial agent

The bark of the cinchona tree, chewed or made into an infusion to treat febrile illnesses, was probably long known by the Inca before it first attracted European attention. In 1630, Juan Lopez, a Jesuit, 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 that time, malaria was endemic in the Iberian Peninsula and southern Europe and the new treatment was steadily accepted for the treatment of ague.¹

In 1765, Surgeon James Lind RN described the specific use of the powdered bark in an attempt to reduce the indiscriminate use that had developed following its listing in the London Pharmacopoeia by 1677. In 1820, Pelletier and Caventou isolated the alkaloids quinine and cinchonine. This allowed accurate dose prescribing and assay of alkaloid content in bark lots.²

The next milestone in the development of antimalarial agents 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.² This diversified the production of cinchona alkaloids, making a potential control for the ague infecting military and trade missions to the East Indies. Within 50 years Javanese plantations produced most of the world's supply of cinchona alkaloids.³

In 1926, the first synthetic antimalarial agents were developed through clinical trials by German pharmaceutical companies (8-aminoquinolines and pamaquine). Following these compounds were primaquine and the 4-aminoquinolines, which led to ontoquine and chloroquine.⁴

In December 1941, Japan invaded Malaya and the Indonesian archipelago, gaining control of most of the cinchona plantations supplying quinine to the rest of the world.³ The supply of

Synopsis

- ◆ The development of synthetic antimalarial drugs was given an urgent start in the Second World War when Japan captured the world's main supplies of quinine in Java. Mepacrine and chloroquine were the chief agents developed at that time.
- ◆ Since the Second World War, the development of chloroquine-resistant falciparum malaria has driven the search for new drugs.
- ◆ Mefloquine, developed by the Walter Reed Army Institute of Research in the United States, was first shown to be effective for prophylaxis and treatment of resistant falciparum malaria in the 1970s.
- ◆ Mefloquine acts on the blood stages of the *Plasmodium* life cycle after the release of merozoites from the liver. It does not have tissue schizonticidal activity, and so does not "cure" those forms of malaria retaining late liver stages (hypnozoites). It does not act against the sexual stages taken up by the mosquito in the life cycle, and therefore does not block transmission.
- ◆ Mefloquine is associated with neuropsychiatric and gastrointestinal adverse reactions, but no more so than other antimalarial drugs.
- ◆ Dosage regimens for mefloquine prophylaxis are simpler than other comparably effective regimens.
- ◆ Australian military experience with mefloquine for malaria chemoprophylaxis is limited, but the drug merits consideration as an alternative to the currently recommended regimen.

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quinine to the Western Alliance was severely restricted. Non-battle casualties among Australian and British forces in New Guinea and Burma during the ensuing campaign were crippling. The Australian Army Land Command responded by raising the Medical Research Unit (IMRU) under Colonel Neil Hamilton Fairley.⁵

IMRU was particularly successful in developing Atabrine (mepacrine) for operational use in the New Guinea campaigns. This unit was the forerunner of the present Army Malaria Institute.

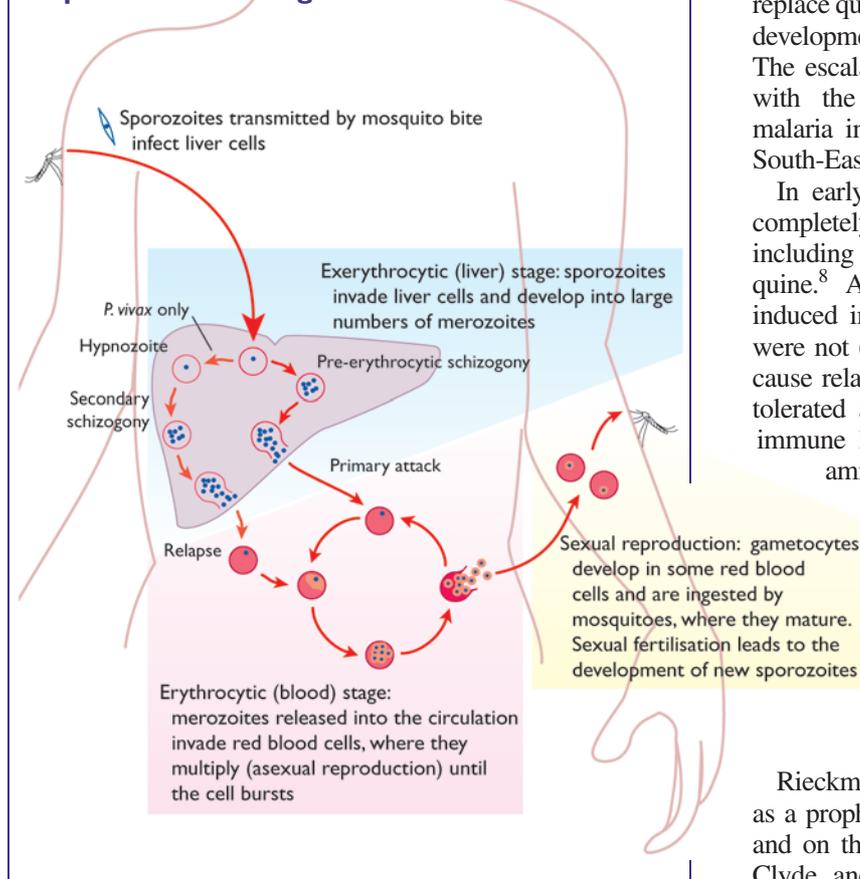
As has become a recurring theme in the development of antimalarial agents, military events and the potential for increasing non-battle casualties stimulated research and development. Wellcome Pharmaceuticals rediscovered data held on ontoquine and chloroquine.¹ In the United States, the Walter

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I: The simplified life cycle of the *Plasmodium* parasites infecting humans



against the liver hypnozoites of *Plasmodium vivax* and therefore do not prevent relapses of vivax malaria.

Much of the research into blood schizonticidal agents to replace quinine, and particularly chloroquine, was driven by the development of *P. falciparum* malaria resistant to chloroquine. The escalation of preclinical trials with WR30090 coincided with the appearance of chloroquine-resistant falciparum malaria in areas of military interest to the United States in South-East Asia and South America.³

In early clinical trials, WR30090 was well tolerated and completely cleared blood schizonts of falciparum malaria, including strains moderately and highly resistant to chloroquine.⁸ Against vivax malaria, 86% (6/7) of trophozoite-induced infections were cleared, while sporozoite infections were not (as WR30090 does not affect the tissue phases that 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 falciparum malaria, and the New Guinea

Chesson and Vietnam strains of vivax malaria.⁹ Consequently, WR30090 was taken to Thailand for treatment trials directly against known chloroquine-resistant falciparum malaria. The drug was effective against malaria, but produced a series of neurological and gastrointestinal adverse events and was cumbersome to use.¹⁰ Subsequently, WRAIR developed WR142490 (mefloquine).¹¹

Rieckmann et al first published on the efficacy of mefloquine as a prophylactic agent against falciparum malaria in 1974,¹² and on the treatment of malaria with mefloquine in 1975.¹³ Clyde and colleagues reported the suppressive activity of mefloquine against sporozoite-induced infection in human volunteers in 1976.¹⁴ Mefloquine was quickly found to be effective against known resistant strains of falciparum malaria, including those isolated in the South-East Asian region,¹⁵ and became the standard treatment for such cases.¹⁶ In the 10 years after these initial pre-registration trials, Phase II and III field trials continued to show the effectiveness of mefloquine in areas of known chloroquine-resistant falciparum malaria in Africa,¹⁷ South-East Asia,^{18,19} China²⁰ and South America,²¹⁻²³ including in children with complicated malaria.²⁴ Some trials also indicated equivalent efficacy with chloroquine in treating vivax malaria.²⁵

Clinical evidence of parasites resistant to mefloquine began to appear in the Australasian region around the time of the drug's general availability in 1985.²⁶ With increasing resistance in Africa and India, strategies to "protect" new agents such as mefloquine were suggested²⁷ 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,²⁶ although the combination did become the preferred therapeutic option in areas of known or suspected mefloquine resistance in Asia²⁸ and Africa.²⁹

Reed Army Institute of Research (WRAIR) increased development efforts on chloroquine following the success of mepacrine,⁶ as well as continuing further research into means of prolonging the antimalarial effects of cinchona alkaloids.⁵

Following the Second World War, several allied nations became involved in land wars in South-East Asia and again sustained non-battle casualties from malaria. At this time, it was noted that cinchonine and quinine 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.⁷

After the end of the Second World War, about 120 compounds were produced at WRAIR in this line of research to find replacements for quinine. An early compound taken to field trials was WR30090, representing the class 2-phenyl-4-quinolinemethanol, the second generation of quinolinemethanols from quinine and the cinchona alkaloids.⁷ This class of antimalarial drugs developed by WRAIR were blood schizonticides, useful in suppressive chemoprophylaxis and in radical cure of non-relapsing (non-vivax) malaria. However, as these compounds have no effect against the pre-erythrocytic hepatic stage of any of the plasmodial species, they do not provide true causal prophylaxis against malaria. They are also inactive

Current recommended use of mefloquine

Mefloquine acts on the blood stages of the *Plasmodium* life cycle after the release of merozoites from the liver in all four species of malaria infecting humans.³ It does not have tissue schizonticidal activity and so does not “cure” those forms of malaria retaining late liver stages (hypnozoites), as occurs in the life cycle of *P. vivax* and *P. ovale*.⁷ Similarly, it does not act against the sexual stages taken up by the mosquito in the life cycle, and therefore does not block transmission.

The recommended regimen for malaria prophylaxis with mefloquine is 250mg weekly, beginning three weeks before exposure. For treatment, the dose of mefloquine ranges from 15mg base/kg in semi-immune patients to 25mg base/kg in non-immune patients.³ The ADF follows a split-dose regimen of 15mg/kg given in three doses (750mg, followed by 500mg six hours later, then 250mg a further six hours later) to reduce adverse effects.³⁰

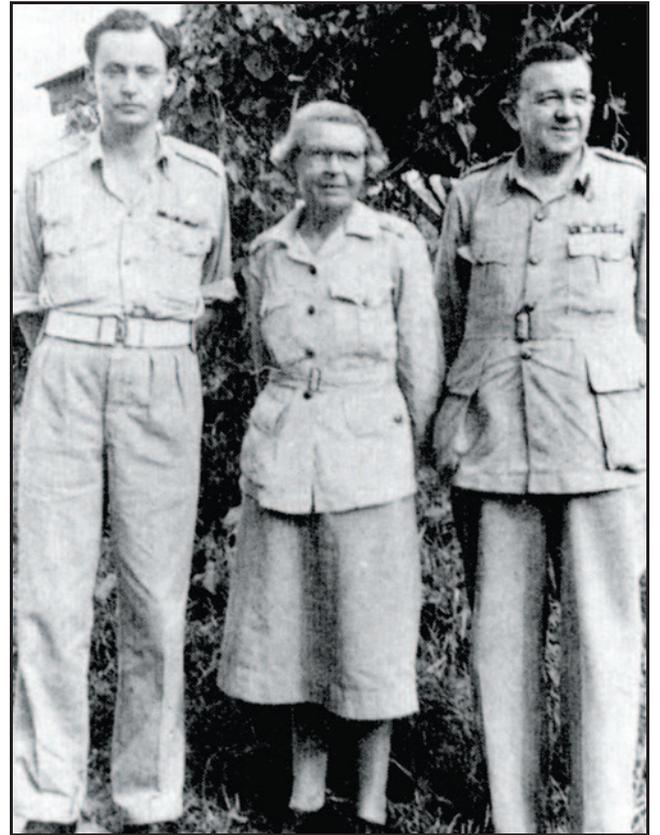
Recent military use of mefloquine

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 1992.³¹ Even though compliance with chemoprophylaxis 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 battalions of Dutch marines using mefloquine chemoprophylaxis had suffered 31 falciparum malaria infections during their deployment to Cambodia during 1992–1993.³² 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. After detailed surveillance of the final group, the Dutch nevertheless concluded that mefloquine was “well tolerated”, though not totally effective.³³

For the British, Croft made the point that mefloquine toxicity was comparable to that of other forms of chemoprophylaxis currently in use.³⁴ He later demonstrated that the incidence of severe neuropsychiatric events was less than one in 6000 soldiers exercising in Kenya,³⁵ and that British soldiers on exercise did not report any more adverse effects from mefloquine than from the combination of chloroquine and proguanil.³⁶

More information about the use of mefloquine under military operational conditions arose from military peace-keeping operations in East Africa. Between December 1992 and May 1993, 9000 US troops were deployed to Somalia, sustaining 48 casualties from malaria.³⁷ Risk factors identified were non-compliance with chemoprophylaxis (doxycycline and mefloquine). Mefloquine effectiveness in the region was incomplete, as five casualties were found to have had suppressive serum



2: Brigadier Neil Hamilton Fairley (right), first commander of the Medical Research Unit (1MRU) raised in 1942 to combat malaria in Australian troops. With him are Lieutenant Colonel Charles Ruthven Blackburn and Major Josephine Mackerras.

mefloquine levels on diagnosis of malaria. Because doxycycline has a short half-life, inadequate serum levels could not be confirmed. One year after the operation had begun, the US military had imported 112 cases of malaria.³⁸ On interview, 56% of these subjects reported compliance with chemoprophylaxis; however, 50% of the group interviewed had been prescribed inadequate doses 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.³⁹ These were pleasing results in light of the British experience in Kenya.³¹ However, chloroquine with proguanil began to fail the Italian forces, as they sustained 100 malaria casualties in the first three months of deploying 4800 peacekeepers to Mozambique 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 casualties to 19 in the last two months of the operation.³⁹ 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.⁴⁰

Brazilian peacekeepers deployed to Angola for six months in 1995–1996 used mefloquine 250mg weekly for malaria chemoprophylaxis.⁴¹ Despite this 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 chemoprophylactic agent was needed for military forces, despite the finding of poor and erratic compliance as the major risk factor for contracting malaria.

In another collaboration with the US military, non-immune Indonesian soldiers posted to 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.⁴² The soldiers tolerated mefloquine chemoprophylaxis well and experienced complete efficacy with the regimen. Notably, mefloquine was not open label in this trial. This is comparable to the findings of earlier studies by the US AFRIMS group with the Royal Thai Marines on the Thai-Cambodia border, among whom mefloquine was well tolerated and compliance readily achieved (91%).⁴³

The Australian military experience with mefloquine is limited, as doxycycline 100mg daily has been the main chemoprophylaxis regimen since replacing chloroquine and Maloprim in the early 1990s. After increasing failure of this combination regimen under field conditions in Papua New Guinea, it was changed to doxycycline 50mg daily with chloroquine 300mg weekly.⁴⁴ Various combinations of chemoprophylaxis were considered and tested, including mefloquine 250mg weekly, which was found to be completely effective in protecting a small group of 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 alternative to doxycycline 100mg daily for short-term exposures in malaria-endemic areas.³⁰ It was used in this capacity for those intolerant of doxycycline during Australian deployments to Cambodia and Somalia and exercises in Papua New Guinea, although numbers of personnel using this regimen were very small.^{30,45}

Conclusions

The development of mefloquine was closely aligned with military needs. This biodefence agent addresses the operationally relevant malaria species, *P. falciparum*, and drug-resistant phenotypes of this species. It has an operationally suitable frequency of dose. The shortcomings of mefloquine have been the adverse event profile on the background of military use, particularly neuropsychiatric events, and limitations in suppressive management of vivax malaria. In terms of a biodefence system, these are not critical, as they are reasonably predictable and manageable.

While chemoprophylaxis remains the cornerstone of malaria casualty control, attention will always need to be paid to compliance. With comparable attention to tailoring mefloquine

use as that paid to appropriate uniform fit or weapon allocation, most service personnel will be well protected with mefloquine during military operations in malarious areas.

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History

“Kirkpatrick’s” — a Simpson memorial with a difference

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THERE ARE MANY MEMORIALS to John Simpson Kirkpatrick (1892–1915), the famous Anzac stretcher-bearer remembered in the phrase “Simpson and his Donkey”. The most revered is his headstone at the Beach Cemetery, Anzac Cove. Simpson’s grave is perhaps the spot most visited by Australians and New Zealanders today who make the pilgrimage to Gallipoli. But there is another memorial to Simpson that is

much frequented — a public house in South Shields, Tyneside, named “Kirkpatrick’s” in his honour. The pub, opened in 1990, stands beside a bronze statue of Simpson and his donkey that was erected in 1988, Australia’s bicentenary year.

There can be little doubt that the man himself would have approved of a pub as a memorial. Before his service at Anzac Cove in April and May, 1915, Jack Kirkpatrick (as he signed himself) had been a ship’s stoker, a cane cutter in north Queensland and a coalminer in New South Wales.¹ It was a rough life. In a letter to his mother dated 7 January 1912, he described how he and his fellow stokers (of the SS *Kooringa*) became inebriated in Melbourne on 25 December 1911, and had enjoyed a violent fracas:

We had goose and Plum Pudding and brandy sause [*sic*] and of course we drank each others health quite a number of times until each man thought he was Jack Johnson champion of the world then my mate suggested going over and having a fight with the sailers [*sic*] of course that was heriled [*sic*] as a noble idea and as the sailers feeling a bit lively themselves from sampling the bottle too much things went pretty lively for the next half hour. You couldn’t see anything for blood and snots flying about until Mates and Engineers came along and threatened to log all hands forward...we all had trophies of the fray someone bunged one of my eyes right up and by the look of my beak I think someone must have jumped on it in a mistake when I was on the floor but as they say alls well that ends well ...”

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