Mefloquine to prevent malaria: a systematic review of trials

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Abstract

Objective: To evaluate the research evidence on the efficacy and tolerability of mefloquine chemoprophylaxis.

Search strategy: Any potentially relevant trial from the Cochrane Infectious Disease Group's register of controlled trials; systematic searches of Medline, Embase, Lilacs and Science Citation Index; scanning citations; and consulting drug companies and key investigators. We considered studies in all languages.

Inclusion criteria: Trials carried out in non-immune adult travellers, and in non-travelling volunteers, where an attempt had been made to conduct a randomised comparison of mefloquine against placebo or against alternative standard prophylaxis.

Results: 37 potentially eligible trials of mefloquine prophylaxis were identified, and 10 met the inclusion criteria. These 10 trials comprised a total of 2750 non-immune adult participants randomised to mefloquine or to a control. One placebo controlled trial examined malaria incidence directly and showed mefloquine to be highly effective in preventing malaria in an area of drug resistance. However, four placebo controlled trials showed that mefloquine was not well tolerated, and withdrawals were consistently higher in mefloquine treatment arms than in placebo arms (odds ratio 3.49 (95% confidence interval 1.42 to 8.56)). Five field trials compared mefloquine with other chemoprophylaxis. Mefloquine was no worse tolerated than other chemoprophylaxis, although there was possibly a trend towards higher withdrawals in mefloquine arms (odds ratio 1.33 (0.75 to 2.36)).

Conclusion: One trial showed mefloquine to be effective in preventing malaria, but withdrawal rates, presumably from side effects, were high across most studies. This is likely to impair mefloquine's effectiveness in general travellers, and it may therefore not be useful for routine prophylaxis. Mefloquine may be useful in specific situations such as for groups travelling to regions with a high risk of chloroquine resistant malaria and only limited access to effective medical care.

Introduction

Travellers from temperate climates who visit regions where infection with *Plasmodium falciparum* is endemic are at particular risk of morbidity and mortality. Chemoprophylaxis with an antimalarial drug is generally recommended, in addition to simple measures to avoid mosquito bites. Resistance of some malarial parasites to common antimalarial drugs has meant that doctors recommend a variety of other drugs and drug combinations. However, some drugs have serious side effects, and identifying the optimal prophylactic regimen requires careful assessment of the best available research evidence.

Mefloquine first became available for European travellers in 1985, as Lariam, and is now widely recommended for antimalarial chemoprophylaxis.¹⁻⁶ It is a

relatively expensive drug.^{7,8} Official acceptance of the tolerability of weekly mefloquine prophylaxis was founded on two uncontrolled, observational studies that were published within three months of each other in a prestigious journal.^{9,10} The tolerability is now in doubt, with more recent observational data showing an excess of neuropsychological side effects in travellers taking mefloquine compared with travellers taking other standard chemoprophylaxis.¹¹⁻¹⁴ Recent anecdotal evidence suggesting that mefloquine is more toxic in chemoprophylaxis than was previously recognised has fuelled the debate about its safety.^{15,16} The controversy has been particularly acute in Britain, Canada, and the Netherlands and has prompted parliamentary questions and intense media interest.

We conducted a systematic review to assess the evidence from randomised controlled trials of the effectiveness of mefloquine in preventing malaria infection in non-immune adult travellers.

Methods

Inclusion criteria

The type of study, intervention, and participants were prespecified as any chemoprophylaxis study in which an attempt had apparently been made to conduct a randomised comparison between mefloquine (or a combination of mefloquine and some other prophylactic drug or drugs) and placebo or no drug or an alternative standard regimen. We excluded studies if either the experimental or the control arm comprised a regimen no longer used for prophylaxis because of severe side effects (such as mefloquine-sulfadoxine-pyrimethamine, sulfadoxine-pyrimethamine, and amodiaquine). Eligible participants were adults not immune to malaria who were travelling to endemic malarious regions and were given short term drug regimens (< 12 months) to protect them from malaria infection. Randomised trials of toxicity carried out on pretravel or non-travelling volunteers were also eligible for inclusion.

Search strategy

The Cochrane Infectious Disease Group's register of randomised controlled trials uses standard methods for identifying trials and was the main source of studies.^{17,18} We conducted additional searches of Medline, Embase, and Lilacs databases from 1966 onwards using a highly sensitive search strategy¹⁷ and the terms "malaria" and "prevention" and "malaria" and "prophylaxis". We applied no language restrictions. We checked the Science Citation Index regularly and sought additional published and unpublished trials by scanning the citations in all retrieved articles, by approaching drug companies for details of unpublished studies, and by corresponding with authors and investigators active in the subject of malaria chemoprophylaxis.

Efficacy and tolerability

We analysed outcomes according to primary and secondary evidence of efficacy (malarial illness confirmed by positive smear and antibody markers of recent plasmodium infection, respectively) and primary and secondary evidence of general tolerability (discontinuation of or poor compliance with study regimen, and reported symptoms and deaths or hospitalisations not from malaria). Out of the various outcomes reported by investigators, we considered that pooling of data on withdrawals and non-compliance provided the best scientific evidence of drug tolerability.

To facilitate comparisons of tolerability between mefloquine and other regimens, we analysed three separate categories of symptoms: neuropsychological, gastrointestinal, and "other." Most authors reported "neuropsychiatric" effects of mefloquine. However, as few of the trial participants actually sought formal medical assistance, the term "neuropsychological" is more correct and is the generic descriptor we have used for this group of symptoms. For the neuropsychological and gastrointestinal categories, we analysed only the five most commonly reported symptoms. These were: depression, dreams, fatigue, headache, and insomnia (neuropsychological); and abdominal discomfort, anorexia, diarrhoea, nausea, and vomiting (gastrointestinal). The two "other" symptoms we analysed were fever and pruritus.

Some of the studies we identified included objective tests of psychomotor performance and neurobehavioural status. These studies were primarily designed to answer specific questions about participants' preservation of technical skills (such as flying or driving) while taking mefloquine and not to assess the efficacy and general tolerability of the drug. We therefore did not include these outcomes in our analysis.

In addition to manually extracting data from published versions of the studies, we wrote twice to first authors asking them to supply data on outcomes that they had not reported in print or not reported on fully. Half responded. We are unable to assess whether non-response indicated any bias in the published data by authors or simply reflected other priorities that researchers might have on their time.

Results

We identified 37 trials of mefloquine chemoprophylaxis carried out between 1970 and 1997, of which 10 met the inclusion criteria.¹⁹⁻³¹ The table summarises the characteristics of these 10 trials, two of which are currently unpublished.^{24 28} Details of all 37 trials are available in the *Cochrane Library*.¹⁸

The 10 trials included represented a total of 2750 non-immune adult participants randomised to mefloquine prophylaxis or to a control. Five of the trials were carried out as clinical toxicity studies in non-travellers. Five were field studies carried out in military personnel, who were almost exclusively male. The intensity of exposure to malaria in these five field trials ranged from nil with Boudreau et al²¹ to high with Ohrt et al.²⁹ Only Ohrt and colleagues' trial yielded cases of malaria with positive smears.

In nine of the trials adequate measures had been taken to conceal allocation to the mefloquine or control arm.^{19-26 28-31} One trial was unblinded.²⁷

In five of the trials an adequate method was specified for generating random assignments.^{19 20 22-26 29} In four of the remaining five trials the allocation method was generated by a method that was unclear from the authors' description but which was described as being random.^{27 28 30 31} In one study the allocation sequence seemed to have been generated by a method that was non-random but unbiased.²¹

All 10 trials carried out an intention to treat analysis and had few or no losses to follow up. Only two published trials included detailed reporting of the symptoms experienced by all participants, although even here there were omissions.^{27 29} The reporting of symptoms in the placebo controlled trials was in most cases incomplete. For these trials, we were able to analyse only two reported symptoms: sleep disturbance and diarrhoea.

Mefloquine compared with placebo

Five trials compared outcomes between mefloquine and placebo.^{26 28-31} One trial of soldiers in Irian Jaya showed mefloquine to be highly efficacious (no cases in 202 person-months of exposure) compared with placebo (53 cases in 109 person-months of exposure).²⁹ Although the numbers in each study were small, the four placebo controlled trials reporting withdrawals showed that the participants taking mefloquine were more likely to withdraw formally from the study than those taking placebo (odds ratio 3.49 (95%

Details of 10 randomised controlled trials of mefloquine chemoprophylaxis in non-immune adults

Type of study	Participants	Comparison arms	No of participants
Arthur et al ^{19 20}			
Field trial, Thailand	American soldiers*	Mefloquine weekly	134
		Doxycycline daily	119
Boudreau et al ²¹			
Field trial, Hawaii	American marines*	Mefloquine loading dose regimen	46
		Mefloquine weekly	157
		Chloroquine weekly	156
Croft et al ^{22 23}			
Field trial, Kenya	British soldiers*	Mefloquine weekly	317
		Chloroquine weekly + proguanil daily	307
Croft et al ^{24 25}			
Field trial, Kenya	British soldiers	Mefloquine weekly	275
		Chloroquine twice weekly + proguanil daily	268
Davis et al ²⁶			
Clinical toxicity study, Australia	Non-travelling volunteers	Mefloquine weekly	46
		Placebo weekly	49
Kollaritsch et al ²⁷			
Clinical toxicity study, Austria	Non-travelling volunteers	Mefloquine weekly	60
		Chloroquine weekly	60
Macpherson et al ²⁸			
Clinical toxicity study, Canada	Pre-travel volunteers	Mefloquine loading dose regimen	251
		Placebo	238
Ohrt et al ²⁹			
Field trial, Indonesia	Indonesian soldiers*	Mefloquine loading dose regimen	68
		Doxycycline daily	67
		Placebo	69
Schlagenhauf et al ³⁰			
Clinical toxicity study, Switzerland	Swissair trainee pilots	Mefloquine loading dose regimen	23†
		Placebo	
Vuurman et al ³¹			
Clinical toxicity study, Netherlands	Non-travelling volunteers	Mefloquine loading dose regimen	20
		Placebo	20

*Participants were exclusively male.

†Participants served as their own controls.

Withdrawal of participants from 10 trials of mefloquine chemoprophylaxis compared with placebo or alternative chemoprophylaxis

confidence interval 1.42 to 8.56)) (see fig).²⁸⁻³¹ The absolute risk of withdrawal, based on pooled withdrawal rates, was 3.3% (4.4% – 1.1%) (95% confidence interval 0.6% to 6.0% using the Yates' continuity correction).

Analysis of secondary evidence of tolerability in the placebo controlled trials revealed a trend consistent with mefloquine being more toxic than placebo for at least two physiological parameters (sleep disturbance and diarrhoea). However, the number of participants was small, and the differences were not significant (odds ratios 8.11 (95% confidence interval 0.80 to 82.13) and 1.95 (0.81 to 4.72) respectively).

Mefloquine compared with alternative chemoprophylaxis

Six trials compared outcomes between mefloquine and alternative chemoprophylaxis.^{19-25 27 29} Of these, only one measured relative incidence of malaria: Ohr et al studied Indonesian soldiers in an area of high malaria transmissibility and found no cases of malaria in the 68 participants taking mefloquine compared with one case in the 67 participants taking doxycycline.²⁹

There was no obvious or significant difference in non-compliance at first assessment in the pooled data across the four trials that measured this (odds ratio 1.04 (0.69 to 1.58)).^{19 20 22-25 29} There was a trend towards higher withdrawals in mefloquine arms (odds ratio 1.33 (0.75 to 2.36)), even though the absolute risk of withdrawal was only 0.95% (3.4% – 2.5%) (95% confidence interval – 0.89% to 2.6%).

Secondary evidence of tolerability from the outcome category "reporting any symptom at first assessment" showed an overall incidence of side effects from mefloquine that was similar to the overall incidence from other chemoprophylaxis (odds ratio 1.0 (0.80 to 1.27)). Mefloquine was more likely to cause insomnia than other standard drugs (odds ratio 1.64 (1.18 to 2.28)) and was more likely to cause fatigue (1.57 (1.01 to 2.45)).

Discussion

The predefined inclusion criteria for this systematic review confined it to controlled trials only. The analysis therefore does not include data on efficacy or tolerability which were reported in observational studies of mefloquine chemoprophylaxis.

The 10 trials included in our review were well designed and carefully executed. There were, however, differences in the scientific methodology of the trials and marked variations in the completeness of reporting of results. Not all trials, for example, included detailed reporting of withdrawals from prophylaxis. This diversity of methodology sometimes made the extraction and synthesis of data on outcomes difficult.

Our review identified only one field trial that included primary evidence of the efficacy of mefloquine in preventing malaria.²⁹ This trial showed mefloquine to be much more efficacious than placebo, and more efficacious than doxycycline in an area with drug resistant malaria.

Five trials assessed the tolerability of mefloquine compared with placebo, and withdrawal was greater in the mefloquine arm.^{26 28-31} This is consistent with anecdotal reports of unpleasant side effects from mefloquine.

In the five field trials, all of which were in soldiers and which compared mefloquine with other chemoprophylaxis, withdrawals tended to be higher in the participants taking mefloquine.^{19-25 29} Although the pooled estimate of effect relative to other regimens was not significant, we would surmise that adherence in soldiers to chemoprophylaxis tends to be unusually high for all regimens because of the military ethos of obedience to orders. Observational data support this hypothesis. Held et al found that travellers who were part of an organised group were more compliant with their malaria prophylaxis than were lone travellers or businessmen.³²

In using pooled withdrawal rates as our primary index of drug tolerability, we used what is currently

considered to be the best method.³³ However, we differ from some authors of the trials we included, who assessed the tolerability of their different study regimens through statistical tests of variance between a "basket" of reported symptoms. In our view, this symptom centred approach lacks objectivity and can result in invalid inferences that are derived from the background "noise" of low grade ill health experienced by ostensibly well trial participants, and not from the pharmacological properties of the trial drugs themselves. We accept, however, that withdrawal from chemoprophylaxis also lacks complete objectivity as an outcome, since some trial participants will persevere with their drugs when they should have stopped and vice versa.

Implications for practice and research

Both withdrawal from, and non-compliance with, malaria prophylaxis are important as they leave travellers incompletely protected. Thus, mefloquine may be highly effective if taken in controlled circumstances by fit young men who are not experiencing unusual psychological stresses. For general travellers, however, mefloquine prophylaxis may be less effective than alternative chemoprophylaxis that is better tolerated.

Observational data suggest that general travellers are more likely than soldiers, especially male soldiers, to withdraw from mefloquine prophylaxis and that they are also inherently more likely to suffer toxicity from the drug. Huzly et al have shown that travellers with chronic disorders are significantly more likely to report side effects from their antimalarial drugs than are healthy travellers.³⁴ Recent observational studies have consistently found that women more commonly report side effects from mefloquine chemoprophylaxis than do men,^{12 14 35-37} and one study has shown that adult women experience roughly twice the toxicity from mefloquine treatment as do adult men.³⁸ Some authors have hypothesised that the physiological and psychological stresses of intercontinental travel, such as would probably affect general travellers more than soldiers undergoing peacetime military training, may act as a "substrate" for mefloquine-associated neurotoxicity.^{26 30 37 39}

The above observations suggest that general travellers experiencing the normal stresses of intercontinental travel would report mefloquine related symptoms to a higher degree than did the exclusively military (and overwhelmingly male) participants in the field trials analysed here. This hypothesis, however, has not been tested experimentally.

Conclusions

Our systematic review generates sufficient uncertainty over tolerability, as detected in high withdrawal rates in placebo controlled trials, to suggest that the effectiveness of mefloquine prophylaxis will be limited by low adherence. However, the evidence from field trials among military personnel of higher withdrawal rates from mefloquine compared with other antimalarial drugs is less strong. Our opinion, based on the best evidence to date, is that the usefulness of mefloquine in prophylaxis is limited to fit, highly motivated occupational subgroups or individual travellers at high risk of infection with chloroquine resistant *Plasmodium falciparum*. Even for these travellers, mefloquine should be prescribed only when the travel destination is one

Key messages

- We conducted a systematic review of the effectiveness of mefloquine in malaria chemoprophylaxis and found 10 randomised controlled trials of the drug in non-immune adult participants
- In placebo controlled trials rates of withdrawal were significantly higher from mefloquine treatment, suggesting that the effectiveness of chemoprophylaxis may be limited by low adherence
- Five field trials of mefloquine prophylaxis were conducted in non-immune participants, but all were young, fit soldiers, so that the findings of these field trials may not be generalisable to the normal population of general travellers
- National malaria prevention guidelines should be evidence based, and candidate antimalarial drugs should not be licensed for routine use in prophylaxis until field trials in general travellers of both sexes have confirmed the tolerability of the new regimen

where reliable diagnostic and treatment facilities are not readily available.

Mefloquine prophylaxis has been prescribed to over eight million travellers worldwide.⁴⁰ It is therefore surprising that not one randomised controlled trial has assessed the tolerability of mefloquine chemoprophylaxis in a heterogeneous study population of non-immune tourists and business travellers. The public are now justifiably concerned about the safety of this drug, and the absence of relevant research makes it difficult for doctors to reassure or advise them in an informed and convincing way.

The controversy surrounding mefloquine shows that, at an international level, there is a need for appropriate research to be done and used to develop valid, evidence based guidelines on malaria prevention through an appropriately multidisciplinary advisory panel. Such a panel should use rigorous and predefined criteria for synthesising the best available research evidence.⁴¹⁻⁴⁵ The panel should optimally consist of six to ten members, of whom at least one should be a primary care physician.^{46 47} The evidence based guidelines produced by this international panel should then be translated into national recommendations, both internally valid and externally reproducible. Consumers in each country should have ready access to the guidelines, and to a summary of the supporting evidence, so as to be empowered to make informed choices about their own health.^{42 48 49}

Trials of mefloquine are required, but the widespread public concern in Britain, Canada, and the Netherlands over Lariam will make it difficult to implement them in these countries. As a lesson for the future, no candidate antimalarial agent should be licensed for routine use in prophylaxis until at least one large randomised controlled field trial has been carried out in general travellers. This trial should be of appropriate design and of sufficient power to show that the new compound is well tolerated by the target population under the anticipated conditions of use.⁵⁰

Future trials of malaria chemoprophylaxis should use a standardised scientific methodology⁵¹ and should be reported completely, in accordance with the CONSORT guidelines on the better reporting of randomised controlled trials.⁵²⁻⁵⁴ Withdrawals from prophylaxis, and poor or non-compliance, should be reported as primary outcomes.

This is a shortened version of a systematic review that is to be published in full in the *Cochrane Library* (Update Software, PO Box 696, Oxford, OX2 7YX) on 13 January 1998.

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Endpiece Alternative definitions

Conversation: A fair for the display of minor mental commodities, each exhibitor being too intent upon the arrangement of his own wares to observe those of his neighbour.

Ambrose Bierce, *The Cynic's Word Book* (1906), subsequently titled *The Devil's Dictionary*