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Hypothesis

Adverse effects of the antimalaria drug, mefloquine: due to primary liver damage with secondary thyroid involvement?

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Abstract

Background: Mefloquine is a clinically important antimalaria drug, which is often not well tolerated. We critically reviewed 516 published case reports of mefloquine adverse effects, to clarify the phenomenology of the harms associated with mefloquine, and to make recommendations for safer prescribing.

Presentation: We postulate that many of the adverse effects of mefloquine are a post-hepatic syndrome caused by primary liver damage. In some users we believe that symptomatic thyroid disturbance occurs, either independently or as a secondary consequence of the hepatocellular injury. The mefloquine syndrome presents in a variety of ways including headache, gastrointestinal disturbances, nervousness, fatigue, disorders of sleep, mood, memory and concentration, and occasionally frank psychosis. Previous liver or thyroid disease, and concurrent insults to the liver (such as from alcohol, dehydration, an oral contraceptive pill, recreational drugs, and other liver-damaging drugs) may be related to the development of severe or prolonged adverse reactions to mefloquine.

Implications: We believe that people with active liver or thyroid disease should not take mefloquine, whereas those with fully resolved neuropsychiatric illness may do so safely. Mefloquine users should avoid alcohol, recreational drugs, hormonal contraception and co-medications known to cause liver damage or thyroid damage. With these caveats, we believe that mefloquine may be safely prescribed in pregnancy, and also to occupational groups who carry out safety-critical tasks.

Testing: Mefloquine's adverse effects need to be investigated through a multicentre cohort study, with small controlled studies testing specific elements of the hypothesis.

Background

Mefloquine was developed by the US Army and introduced for the treatment of malaria in the late 1970s. [1] Mefloquine was first used for prophylaxis in 1985, and since then approximately 14.5 million people have been prescribed the drug for malaria prevention, versus 1.6 million for treatment. [2]

In the first decade of mefloquine's use, the reported adverse effects were mainly gastrointestinal.[3] In the late 1980s it became clear that mefloquine could cause neu-

ropsychiatric adverse effects.[4] The first randomised controlled trial of mefloquine prophylaxis in heterogeneous, non-immune Western travellers was published in 2001 and found that one-third of all mefloquine users reported neuropsychiatric adverse effects and 6% of all users reported at least one severe adverse event (defined as requiring medical advice).[5]

On the evidence from a case series published in 1992 by the manufacturer, Hoffmann-La Roche, the World Health Organisation (WHO) recommends that travellers with a personal or family history of seizures or manic-depressive illness should not take mefloquine prophylaxis.[6,7] However the Centers for Disease Control and their Canadian equivalent, CATMAT, do not recognise this as a valid contraindication to taking mefloquine.[8]

A recent analysis of spontaneous reports held on the Dutch national pharmacovigilance database suggested that there is a mefloquine syndrome consisting of excessive sweating accompanied by malaise, nausea, diarrhoea, agitation, concentration problems and nightmares.[9]

The aetiology of the adverse effects associated with mefloquine use remains obscure. Ten cohort studies in tourists found that women generally experienced worse side effects from mefloquine than men; [6,10–18] an eleventh did not find this effect.[19] In randomised controlled trials, children have tolerated mefloquine well. [20,21] Surprisingly, one cohort study found that some older adult travellers tolerate mefloquine better than younger adults. [22] It has also been reported that Asian patients tolerate mefloquine better than Caucasians and Africans. [23,24] Despite early concerns, mefloquine appears to be safe in pregnancy.[25]

Although the adverse effects of mefloquine are common, and often serious and long lasting, and the drug has been widely used for over 20 years, no real attempts have so far been made to investigate and explain these effects. A systematic review of mefloquine prophylaxis, performed within the Cochrane Collaboration, now tabulates 516 case reports published in 136 papers between 1976–2000, describing adverse effects from mefloquine at prophylactic and therapeutic dosages.[26]

We retrieved and critically reviewed all the original papers listed in the Cochrane review to clarify the phenomenology of the adverse effects associated with mefloquine, and to look for clues to possibly safer use of the drug.

Analysis of case reports

Common features of the case reports

Of the 516 published case reports of mefloquine adverse effects recorded in the mefloquine systematic review, 328 of the reports related to prophylactic mefloquine use, and 188 to treatment use. 324 of the 516 cases (63%) related to tourists or business travellers.[26] One-third of the reports were in languages other than English – mainly French, German and Danish. The search strategy for finding the case reports is described in the review.[26] An annotated bibliography of the 516 published reports can be found at [http://www.liv.ac.uk/evidence] .

26% of the case reports recorded three or fewer individual patient parameters (for example, the patient's age, sex and mefloquine dose taken), and many of these reports were little more than a short description of an unexpected adverse event, set in the context of a larger study. 52% of the reports however contained some discussion of the causality of the symptoms attributed to the drug, and 11% proposed a mechanism by which these symptoms might be occurring.

56% of the 516 case reports we reviewed described one or more symptoms consistent with a *transient, anicteric chemical hepatitis* (eg, malaise, fever, anorexia, headache, abdominal pain, nausea, diarrhoea, concentration difficulties). Of the remaining reports, many were consistent with a *post-hepatic syndrome*, although in some cases the disorders described could have been due to conditions such as anxiety, depression, chronic fatigue or jet lag.

15% of all the case reports described symptomatology suggesting acutely *disturbed thyroid function* (eg, anorexia, fatigue, tremor, palpitations, nervousness, increased sweating, mood and/or sleep disturbance, memory and concentration disorders, emotional lability, altered bowel habit, depression).

Table 1 categorises the 516 published case reports according to whether the clinical features were 'very likely', 'plausibly' or probably 'unrelated' to liver or thyroid pathology. We have based this classification on standard lists of the common symptoms and signs of liver and thyroid disease. [27,28] The direction of thyroid symptoms was mainly towards hyperthyroidism, though some patients exhibited signs of both an over- and an under-active thyroid (for example, tachycardia alternating with bradycardia).

The table also shows the median duration of symptoms reported by 'prophylactic' and 'treatment' mefloquine users, and the median dose taken within each category. The median duration of adverse effects of patients who took mefloquine as treatment appears to have been shorter than that of those who took the drug as prophylaxis (4 days versus 16 days), even though the median dose of mefloquine taken was higher in the treatment group. We believe that one explanation for this unexpected finding may lie in the fact that the treatment users of mefloquine

Table 1: Clinical features of published case reports of adverse effects from mefloquine, and their possible relation to liver and thyroid pathology

	Prophylaxis case reports (N = 328)	Treatment case reports (N = 188)
Number (%) of reports very likely **liver** related	**75/328***(23)*	**85/188***(45)*
Number (%) of reports plausibly but debatably **liver** related	**102/328***(31)*	**29/188***(15)*
Number (%) of reports plausibly **thyroid** related	**51/328***(16)*	**26/188***(14)*
Probably unrelated to liver or thyroid	**100/328***(30)*	**48/188***(26)*
Median dose (*range*) of mefloquine taken (mg)	**750***(250–8750)*	**1250***(150–5250)*
Median duration (*range*) of adverse effects (days)	**16***(1–550)*	**4***(1–300)*

were more likely to have taken the drug as monotherapy, whereas the prophylaxis users more commonly took one or more co-medications, as well as alcohol. We discuss the possible significance of this later in this paper.

Mefloquine and the liver

Mefloquine is an aryl amino alcohol which accumulates in both the liver and the lungs, and is subject to enterohepatic circulation. [29] It has recently been found to cause acute hepatitis.[30]

Mefloquine does not appear to cause florid signs of liver disease. However, transient subclinical disturbances of liver function are a common feature of many drugs metabolised in the liver, and this may explain the frequent finding of transaminase changes in safety studies of new drugs; these biochemical findings are usually dismissed as meaningless noise, but they may in fact be sensitive or oversensitive markers of vulnerability, of low specificity.

That mefloquine induces liver enzymes is well documented. Jaspers et al reported significantly raised transaminases in Dutch marines who took mefloquine during 3 months in Cambodia, and who were not drinking alcohol at the time. [31] Takeshima found that of a cohort of healthy Japanese soldiers who took prophylactic mefloquine for 36 weeks without drinking alcohol, one-quarter developed symptoms compatible with liver pathology and four showed disturbed liver function. [32] Reisinger et al observed the same phenomenon in a cohort of short-stay European travellers to Africa, but it is not clear whether alcohol could have contributed to this effect.[33] One of the travellers, who was concurrently taking a liver-damaging agent, sulfadoxine,[34] showed gross morphological changes in his liver which were attributed to his use of prophylactic mefloquine. Liver biopsy showed intralobular cellular infiltrates consisting of macrophages and eosinophils as well as sporadic eosinophilic cell necroses; virology was negative. [33] Grieco et al described a 46-year-old woman who drank wine daily while taking mefloquine, and who became nervous and depressed, with nausea, vomiting and diarrhoea. She was dehydrated and in severe liver failure, with negative virology. Liver biopsy showed diffuse macrovesical hepatic steatosis. [35]

'Heavy sun exposure' is noted in a case report of a 60-year-old Frenchman who reacted acutely to his second mefloquine tablet; it is likely that this sun exposure would have caused dehydration.[5] A 20-year old French traveller, concurrently taking an oral contraceptive, had epileptic seizures in her sixth week of mefloquine prophylaxis, directly after 'severe exertion'.[5] It seems likely that in some mefloquine users dehydration will impose an added burden on the liver, and that this could contribute to a severe reaction to the drug. Many long-haul travellers using mefloquine are mildly dehydrated from in-flight alcohol and air conditioning, followed by hot and dry conditions, and more alcohol consumption, at their holiday or business destination.

Of the 516 case reports we reviewed, eleven cited alcohol as possibly contributing to the adverse drug effects described. Wittes et al reported a remarkable challenge-rechallenge experiment where a healthy male geologist took both his third and his fourth weekly mefloquine tablet together with half a bottle of whisky, and on both occasions experienced acute paranoid delusions, depression and suicidal ideation; a fellow geologist who shared the same whisky bottle (and who was taking no antimalaria medication) experienced no such effects.[36]

Vuurman et al, sponsored by Hoffmann-La Roche, tested in healthy volunteers whether or not alcohol might interact adversely with mefloquine.[37] They found psychomotor performance unimpaired, but their study design had important limitations. Only 20 participants took mefloquine and of these, two women dropped out due to adverse events (one with nausea, vomiting and dizziness, the other with malaise, fever and headache). The study protocol forbade 'strenuous physical activity' and any prescribed medications. Alcohol was given under strict laboratory conditions 24 h after mefloquine ingestion, and

then in small and interrupted doses, such that the blood alcohol concentration in any participant never exceeded 0.50 mg ml^{-1}. The authors admit that their study did not address 'the question of what might happen should (mefloquine users) consume intoxicating amounts of alcohol. [37] Their findings can thus not be generalised to the broad population of tourists and business travellers.

Approximately half of the case reports listed in the Cochrane review note some co-medication taken along with mefloquine.[26] Other quinoline derivatives (chiefly chloroquine and quinine) are the commonest co-medications mentioned in the case reports. After antimalaria drugs, an oral contraceptive (noted in 8 reports) is the next most commonly reported co-medication, followed by sodium valproate (7) and diazepam (4). All these drugs can cause liver damage.[34] Diazepam is also a thyroid hormone antagonist, and we discuss below the possible significance of this. Meszaros et al reported a male traveller who in addition to mefloquine took thioridazine, amitriptyline and fluphenazine (all capable of damaging the liver), and whose mefloquine-associated neuropsychiatric symptoms persisted for over a year. [38] Gullahorn et al reported a series of patients who experienced delirium on emerging from anaesthesia, possibly because in addition to mefloquine they had received isoflurane, an anaesthetic known to cause hepatocellular necrosis. [34,39]

One report describes an acute reaction in a man who took one mefloquine tablet each week together with two aspirin tablets. One hour after taking his fifth mefloquine tablet he experienced acute amnesia lasting approximately one hour.[40] Aspirin can cause hepatocellular necrosis,[34] and in addition can aggravate acute thyroid disturbance (discussed below) by competing with thyroid hormones for sites on binding proteins.[53]

Mefloquine and the thyroid

The preclinical studies of mefloquine by the US Army involved close monitoring in animal models and human volunteers of several organ systems, but not the thyroid. [1] The effect of mefloquine on thyroid function appears not to have been investigated in any phase III or phase IV study. Thyroid function has not been tested routinely in the diagnosis or management of patients suffering from mefloquine-related adverse effects.

Thyroid disease, or some possible interference with thyroid activity, is reported in only three of the 516 case reports in the Cochrane review.[26] Bem et al described a 31-year old German woman with a 'thyroid condition', who was also taking 'tranquillisers' (unspecified) and alcohol, and who had an acute exacerbation of her schizophrenia after a single tablet of mefloquine; her symptoms persisted for 4 weeks.[5]Conget et al reported a 30-year old previously healthy woman who experienced abdominal pain, palpitations, instability, insomnia and a fine distal tremor in her second week of mefloquine prophylaxis. A thyroid function screen showed a raised serum thyroglobulin level (54 μg/ml, normal range 18.7 to 27.1); this returned to normal within a month of her stopping mefloquine.[41] Bauer et al reported acute psychotic reactions in a healthy US Peace Corps worker who took prophylactic mefloquine concurrently with diiodohydroxyquinoline for a presumed parasitic infection.[42]

Presentation of the hypothesis

The mefloquine syndrome

The published literature describes a mefloquine syndrome that presents in a variety of ways including headache, gastrointestinal disturbances, nervousness, fatigue, disorders of sleep, mood, memory and concentration, and occasionally frank psychosis. Young western women are particularly vulnerable to mefloquine's adverse effects. Certain groups however (children, older adult travellers and Asian patients) tolerate mefloquine well.

Hypothesis

The phenomenology of mefloquine's adverse effect profile, together with incidental details in some of the published case reports (references to alcohol, and to known hepatotoxic co-medications such as the oral contraceptive pill) suggest that for many mefloquine users adverse drug effects may be the result of primary hepatocellular injury, caused by the drug in association with one or more concurrent liver insults. Further, it seems that in some of these symptomatic users of mefloquine a transient thyroid disturbance may appear as well, either as an endocrine disorder secondary to the primary liver damage, or as an independent pathological process.

We therefore postulate that many of the adverse effects of mefloquine are a post-hepatic syndrome caused by primary liver damage. In some individuals we believe that symptomatic thyroid disturbance occurs, either as an independent process, or as a secondary consequence of the initial hepatocellular injury.

Previous liver or thyroid disease, and concurrent insults to the liver (such as from alcohol, dehydration, an oral contraceptive pill, recreational drugs, and other drugs that can damage the liver) may be related to the development of many severe or prolonged adverse reactions to mefloquine. Co-medications that are thyroid hormone antagonists may also be risk factors.

Relevant reports with other quinoline derivatives

Mefloquine is a synthetic quinoline; other quinolines include primaquine, amodiaquine and chloroquine.[43]

High doses of primaquine in rhesus monkeys have caused acute fatal liver damage.[44]

Amodiaquine is still used to treat malaria, but was withdrawn from general use for malaria prophylaxis in 1986 after it was found to cause liver damage and hepatitis, mostly anicteric. [45,50] Some of these reports mention co-medications known to damage liver cells (phenylbutazone, oral contraceptive, alcohol). [45,46] Amodiaquine has not been linked to disturbed thyroid function.

The possibility of a three-way interaction has already been suggested between a quinoline derivative (chloroquine) and the liver and the thyroid. Munera et al described a woman with hypothyroidism, well stabilised on thyroxine sodium 125 μg daily, who took prophylactic chloroquine and proguanil daily for 2 months for a vacation in Africa.[51] At four weeks her thyroid stimulating hormone (TSH) concentration was found to be very high (44.8 mU/1, normal range 0.35–6.0), but it returned to normal within a week of her stopping the drugs. Re-challenge with chloroquine and proguanil a year later again resulted in raised levels of TSH, a lowered concentration of free triiodothyronine (T_3), and normal free thyroxine (T_4) concentration. Liver function was not tested, but the authors speculated that 'Chloroquine... seems to have enhanced the induction of liver enzymes. [It] probably increased the catabolism of thyroid hormones by enzymatic induction.[51] They also suggested that chloroquine might act centrally on the hypothalamus, through disruption of the feedback system by which thyrotropin releasing hormone stimulates the pituitary to release and later synthesise TSH.[52]

A third mechanism by which chloroquine and chemically related drugs such as mefloquine might interfere with thyroid function is through structural homology to T_3, resulting in thyroid hormone antagonism.[53] In the rat, chloroquine injections more than halve the T_3 concentration, without changing the level of free T_4.[54] Chloroquine has been reported to inhibit T_3 uptake in mammalian cells by inhibiting receptor-mediated endocytosis. [53]

Testing the hypothesis

Our hypothesis needs to be tested through a large multicentre cohort study of mefloquine prophylaxis in tourists and business travellers, perhaps recruited in collaboration with one or more airlines. Small randomised controlled trials should test specific elements of the hypothesis, such as the postulated link between mefloquine and thyroid disturbance, and the presumed interaction between mefloquine and oral contraception. National pharmacovigilance databases should also be analysed systematically to see if the spontaneous reports of mefloquine's adverse effects tend to support our hypothesis or not.

The multicentre cohort study of prophylactic mefloquine use should be questionnaire-based, and should enquire specifically into the major risk factors (alcohol intake during travel, hydration status, use of hormonal contraception and recreational drugs, other potentially hepatotoxic or thyrotoxic drugs, previous history of proven or suspected liver and/or thyroid abnormality) that we have proposed. The study design should include pre- and post-exposure testing of liver and thyroid function in at least a sample of the cohort.

One or more case-control studies should be nested within the cohort study. [55,56] These nested studies would allow for rigorous testing of the aetiological mechanisms which we have proposed for mefloquine's adverse effects. The studies should also resolve those prescribing issues on which experts' opinions differ (eg, Is mefloquine safe in pregnancy? Is it safe for long-term prophylaxis? Should airline pilots be prescribed mefloquine? Should mefloquine be prescribed to people with a personal or family history of neuropsychiatric illness? Can mefloquine be given safely as a pre-travel loading dose, for rapid induction of chemoprophylaxis? [17,57]).

Mefloquine is a clinically important drug, commonly used by healthy people. A much higher standard of safety is therefore required for mefloquine prophylaxis than for drugs given to treat serious diseases.[58,59] The study we propose is urgently needed.

Implications of the hypothesis

What our hypothesis explains

The hypothesis explains much of the complexity of the pattern of adverse effects of mefloquine, and also the fact that many healthy users of the drug suffer no adverse effects at all. It also explains some aspects of mefloquine's tolerability profile in travellers which until now have not been understood, notably that young women experience more adverse effects from mefloquine than men, and that children and older adult travellers (who do not use oral contraception, and who rarely misuse alcohol) seem to tolerate the drug well. In addition, our hypothesis may explain the ethnic and inter individual variations in the pharmacokinetics of this agent, which until now have not been understood. [23,24]

It has been known for some years that mefloquine users who take co-medications are about 1.5 times more likely to experience an adverse drug event than those users who

take no co-medications, and twice as likely to experience severe adverse drug events.[14] The frequency of reported adverse drug events also increases when multiple co-medications are taken.[14] Our hypothesis plausibly explains these earlier findings.

The use of marijuana and other psychoactive agents by chloroquine users has been associated with acute psychotic reactions, and it has been suggested that mefloquine users who take recreational drugs may likewise be predisposed to neuropsychiatric problems.[60,61] We believe that this association is consistent with our hypothesis, since recreational drugs can cause hepatocellular damage and liver failure.[34]

A puzzling observation is that although the adverse effects of mefloquine are usually reversible, in some patients these effects can persist for months or even years after the drug has been stopped.[61] We believe that the occasionally protracted time course of the adverse effects can be plausibly explained by supposing that in these patients mefloquine is just one of several concurrent insults to the liver, and that it is the continuance of the other insults (most commonly alcohol, and certain prescription drugs) that makes the mefloquine-induced syndrome persist. Some published evidence supports this view.[38,62,69] There is evidence from this study (Table 1) that the adverse effects of mefloquine in those who have taken the drug prophylactically persist longer than they do in patients who have been treated with it, even though the latter group mostly receive larger doses of the drug; this paradox might be explained by the fact that although prophylactic users usually stop mefloquine as soon as they have experienced adverse effects, they often continue to assault their livers in other ways, and it is this which makes the effects persist.

Most of the reported adverse effects of mefloquine fit into the model we propose. For example, mefloquine has been associated with a wide variety of dermatological adverse effects, and most of these can be linked with effects on the liver or thyroid.[41,55] Convulsions and dizziness are other reported effects of mefloquine which can be related to liver or thyroid disturbance.[2,41]

Who should not take mefloquine?

We believe that people with a history of any proven or suspected liver or thyroid abnormality in the previous two years should avoid mefloquine. Travellers taking mefloquine should not drink alcohol, especially within 24 h of their weekly mefloquine dose.

While taking mefloquine, travellers should be advised to maintain good hydration with water or carbonated drinks, especially on long plane journeys or during arduous work in hot conditions. Alcohol, tea or coffee should not be used to maintain hydration, since they all increase water loss.

Travellers taking mefloquine should not take a hormonal contraceptive, nor any other drug known to injure liver cells.[34] They should not take any drug known to antagonise thyroid hormone. [53] We propose that drugs that are known to cause hepatocellular injury *and also* to be thyroid hormone antagonists should be absolutely contraindicated in mefloquine users; such drugs include amiodarone, benzodiazepines, calcium channel blockers and phenytoin.[34,53]

Because of the potential for additive toxicity, travellers taking mefloquine should avoid concurrent use of any other quinoline derivative (eg, amodiaquine, chloroquine, primaquine, quinidine, quinine, tafenoquine), whether for additional prophylaxis or for treatment. The administration of a different quinoline derivative at the same time as mefloquine may increase the risk of adverse effects.[70,72] For the same reason, mefloquine users should avoid other quinine analogues, such as fluoroquinolone antibiotics. Fluoroquinolones, such as sparfloxacin, of loxacin and ciprofloxacin, are increasingly prescribed in severe cases of traveller's diarrhoea, and have been associated with severe reactions in mefloquine users. [73]

Who should take mefloquine?

Mefloquine is a safe and exceptionally useful drug for the mass prophylaxis and treatment of those resident populations in malaria-endemic areas which traditionally abstain from alcohol and hormonal contraception. It has been suggested that in such settings, mefloquine should be combined with artemisinin or a derivative to protect both drugs from resistance.[74]

On the basis of our hypothesis, we believe that children, and also pregnant women, can safely be prescribed mefloquine (because neither group uses alcohol or oral contraceptives).

Accompanied by explicit advice to avoid alcohol, maintain good hydration, and use co-medications with caution, we believe that prophylactic mefloquine could be recommended to certain occupational subsets of travellers who carry out safety-critical tasks and who until now have been denied the use of this drug. These occupational groups include airline pilots,[75] divers[76] and operators of heavy machinery.[77]

Some authorities advise that travellers engaged in high-risk leisure pursuits, such as mountain climbing, should not use mefloquine. [78] We believe that this exclusion is

unjustified, as long as there is no recent history of liver or thyroid disease, and provided the precautions we have proposed above (avoidance of alcohol, maintenance of hydration and non-use of hormonal contraception, recreational drugs and certain co-medications) are adhered to.

Lobel et al consider that WHO's exclusion of people with a personal or family history of neuropsychiatric illness from taking mefloquine is based 'on limited evidence or theoretical concerns', and we believe their scepticism is justified.[79] Neuropsychiatric illness may not contraindicate use of mefloquine, provided that the patient is not currently taking anything that can cause liver damage or thyroid disturbance.

Competing interests

None declared.

Table 2: Proposed contraindications to the use of mefloquine

Mefloquine contraindications:

1. Known **hypersensitivity** to the drug.
2. History of any proven or suspected **liver abnormality** within the previous 2 years.
3. History of any proven or suspected **thyroid abnormality** within the previous 2 years, including any concurrent use of thyroid-stabilising medication.
4. Concurrent use of drugs known to cause **hepatocellular injury.** Paracetamol and (especially) aspirin to be used with caution, since both can damage the liver and/or the thyroid.[34,40] Mefloquine users should not take recreational drugs.
5. Concurrent use of **oral contraceptive pill** or **HRT.** Healthcare advisers should recognise that some female travellers will need alternative contraception.
6. Concurrent use of drugs known to be **thyroid hormone antagonists.**[53]
7. Up to 2 units of **alcohol** per day may be taken by users of mefloquine prophylaxis until 24 h before their weekly dose, and from 24 h afterwards.
8. Mefloquine users should avoid concurrent use of **any other quinoline derivative** (eg, amodiaquine, chloroquine, primaquine, quinidine, quinine, tafenoquine), whether for additional prophylaxis or for treatment.

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References

1. Tigertt WD: **The army malaria research program.** *Ann Intern Med* 1969, **70:**150-3
2. Nosten F, van Vugt M: **Neuropsychiatric adverse effects of mefloquine – what do we know and what should we do?** *CNS Drugs* 1999, **11:**1-8
3. Rønn AM, Rønne-Rasmussen J, Gøtzsche P, Bygbjerg IC: **Neuropsychiatric manifestations after mefloquine therapy for *Plasmodium falciparum* malaria: comparing a retrospective and a prospective study.** *Trop Med Int Health* 1998, **3:**83-8
4. World Health Organisation: **Review of central nervous system adverse events to the antimalarial drug mefloquine (1985–1990).** *Geneva: WHO, 1991. Report no: WHO/mal 91.1063.*
5. Overbosch D, Schilthuis H, Bienzle U, Behrens RH, Kain KC, Clarke PD, Toovey S, Knobloch J, Nothdurft HD, Shaw D, *et al*: **Atovaquone-proguanil versus mefloquine for malaria prophylaxis in non-immune travelers: results from a randomized double-blind study.** *Clin Infect Dis* 2001, **33:**1015-21
6. Bem L, Kerr L, Stuerchler D: **Mefloquine prophylaxis: an overview of spontaneous reports of severe psychiatric reactions and convulsions.** *J Trop Med Hyg* 1992, **95:**167-9
7. World Health Organisation: *International Travel and Health.* 2001
8. Schlagenhauf P: **Mefloquine for malaria chemoprophylaxis 1992–1998: a review.** *J Travel Med* 1999, **6:**122-33
9. **Toegenomen transpiratie met mefloquine (Lariam®).** *Geneesmiddelen Bulletin* 1997, **31:**97
10. Weinke T, Trautmann M, Held T, Weber G, Eichenlaub D, Fleischer K, Kern W, Pohle HD: **Neuropsychiatric side effects after the use of mefloquine.** *Am J Trop Med Hyg* 1991, **45:**86-91
11. Barrett PJ, Emmins PD, Clarke PD, Bradley DJ: **Comparison of adverse events associated with use of mefloquine and combinations of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers.** *BMJ* 1996, **313:**525-8
12. Huzly D, Schönfeld C, Beurle W, Bienzle U: **Malaria chemoprophylaxis in German tourists: a prospective study on compliance and adverse reactions.** *J Travel Med* 1996, **3:**148-55
13. Phillips MA, Kass RB: **User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis.** *J Travel Med* 1996, **3:**40-5
14. Schlagenhauf P, Steffen R, Lobel H, Johnson R, Letz R, Tschopp A, Vranjes N, Bergqvist Y, Ericsson O, Hellgren U, *et al*: **Mefloquine tolerability during chemoprophylaxis: focus on adverse event assessments, stereochemistry and compliance.** *Trop Med Int Health* 1996, **1:**485-94
15. Handschin JC, Wall M, Steffen R, Stürchler D: **Tolerability and effectiveness of malaria chemoprophylaxis with mefloquine or chloroquine with or without co-medication.** *J Travel Med* 1997, **4:**121-7
16. van Riemsdijk MM, van der Klauw MM, van Heest JAC, Reedeker FR, Ligthelm RJ, Herings RMC, Stricker BHC, *et al*: **Neuro-psychiatric effects of antimalarials.** *Eur J Clin Pharmacol* 1997, **52:**1-6
17. Micheo C, Arias C, Rovira A: **Adverse effects and compliance with mefloquine or chloroquine + proguanil malaria chemoprophylaxis.** *Proceedings of the Second European Conference on Travel Medicine; 2000 Mar 29–31; Venice, Italy. Venice: Fondazione Cini* 2000
18. Kollaritsch H, Karbwang J, Wiedermann G, *et al*: **Mefloquin-Konzentrationsprofile bei prophylaktischer Dosierung.** *Wien Klin Wochenschr* 2000, **112:**441-7
19. Wolters BA, Bosje T, Luinstra-Passchier MJ: **Niet meer klachten bij mefloquinegebruik dan bij malariaprofylaxe met andere middelen.** *Ned Tijdschr Geneeskd* 1996, **41:**331-4
20. Smithuis FM, van Woensel JBM, Nordlander E, Vantha WS, ter Kuile FO: **Comparison of two mefloquine regimens for treatment of *lasmodium falciparum* malaria on the northeastern Thai-Cambodian border.** *Antimicrob Agents Chemother* 1993, **37:**1977-81
21. Luxemburger C, Price RN, Nosten F, ter Kuile FO, Chongsuphajaisiddhi T, White NJ: **Mefloquine in infants and young children.** *Ann Trop Paediatr* 1996, **16:**281-6
22. Mittelholzer ML, Wall M, Steffen R, Stürchler D: **Malaria prophylaxis in different age groups.** *J Travel Med* 1996, **4:**219-23
23. ter Kuile FO, Nosten F, Thieren M, Luxemburger C, Edstein MD, Chongsuphajaisiddhi T, Phaipun L, Webster HK, White NJ: **High-dose mefloquine in the treatment of multidrug-resistant falciparum malaria.** *J Infect Dis* 1992, **166:**1393-400
24. Phillips-Howard P, ter Kuile FO: **CNS adverse events associated with antimalarial agents.** *Drug Saf* 1995, **12:**370-83
25. Vanhauwere B, Maradit H, Kerr L: **Post-marketing surveillance of prophylactic mefloquine (Lariam®) use in pregnancy.** *Am J Trop Med Hyg* 1998, **58:**17-21
26. Croft AMJ, Garner P: **Mefloquine for preventing malaria in non-immune adult travellers (Cochrane Review).** *In: Cochrane Library.* 2001
27. Finlayson NDC, Hayes PC, Simpson KJ: **Diseases of the liver and biliary system.** *In: Haslett C, Chilvers ER, Hunter JAA, Boon NA, editors. Davidson 's Principles and Practice of Medicine* 1999, 683-736

28. Edwards CRW, Toft AD, Walker BR: **Endocrine disease.** *In: Davidson's Principles and Practice of Medicine* 1999, 543-98
29. Bangchang KN, Karbwang J, Back DJ: **Mefloquine metabolism by human liver microsomes: effect of other antimalarial drugs.** *Biochem Pharmacol,* 1992, **43:**1957-61
30. Gotsman I, Azaz-Livshits T, Fridlender Z, Muszkat M, Ben-Chetrit E: **Mefloquine-induced acute hepatitis.** *Pharmacotherapy* 2000, **20:**1517-9
31. Jaspers CAJJ, Hopperus Buma APCC, van Thiel PPAM, van Hulst RA, Kager PA: **Tolerance of mefloquine chemoprophylaxis in Dutch military personnel.** *Am J Trop Med Hyg* 1996, **55:**230-4
32. Takeshima S: **Side effects with mefloquin for long-term malaria prophylaxis.** *Jpn J Trop Med Hyg* 1994, **22:**193-8
33. Reisinger EC, Horstmann RD, Dietrich M: **Tolerance of mefloquine alone and in combination with sulfadoxine-pyrimethamine in the prophylaxis of malaria.** *Trans R Soc Trop Med Hyg* 1989, **83:**474-7
34. Neuberger J: **Drugs and liver damage.** *In: Oxford Textbook of Medicine* 1996, 2124-30
35. Grieco A, Vecchio FM, Natale L, Gasbarrini G: **Acute fatty liver after malaria prophylaxis with mefloquine.** *Lancet* 1999, **353:**295-6
36. Wittes RC, Saginur R: **Adverse reaction to mefloquine associated with ethanol ingestion.** *Can Med Assoc J* 1995, **152:**515-7
37. Vuurman EFPM, Muntjewerff ND, Uiterwijk MMC, van Veggel LMA, Crevoisier C, Haglund L, Kinzig M, O'Hanlon JF: **Effects of mefloquine alone and with alcohol on psychomotor and driving performance.** *Eur J Clin Pharmacol* 1996, **50:**475-82
38. Meszaros K, Kasper S: **Psychopathologische Phänomene im Langzeitverlauf einer akuten Psychose nach Mefloquinprophylaxe (Lariam®).** *Nervenarzt* 1996, **67:**404-6
39. Gullahorn GM, Bohman HR, Wallace MR: **Anaesthesia emergence delirium after mefloquine prophylaxis.** *Lancet* 1993, **341:**632
40. Castot A, Gamier R: **Réflexion sur les effets secondaires de la méfloquine.** *Concours Med* 1988, **110:**4003
41. Conget JI, Navarro M, Navarro P, Corachán M: **Alteración del perfil hormonal tiroideo tras la administración profiláctica de mefloquina.** *Med Clin (Barcelona)* 1993, **100:**516
42. Bauer WM, Craig CP: **Acute psychotic reactions in an aid worker following separate administrations of mefloquine and iodoquinol.** *Proceedings of the Fifth International Conference on Travel Medicine; 1997 Mar 24–27; Geneva, Switzerland. Geneva: International Society of Travel Medicine,* 1997
43. Nicolas X, Touze JE: **La toxicité cardiaque des antipaludiques.** *Med Trop* 1994, **54:**361-5
44. Schmidt LH, Alexander S, Allen L, Rasco J: **Comparison of the curative antimalarial activities and toxicities of primaquine and its *d* and *l* isomers.** *Antimicrob Agents Chemother* 1977, **12:**51-60
45. Neftel K, Woodtly W, Schmid M, Frick PG, Fehr J: **Amodiaquine induced agranulocytosis and liver damage.** *BMJ* 1986, **292:**721-3
46. Larrey D, Castot A, Pessayre D, Merigot P, Machayekhy JP, Feldmann G, Lenoir A, Rueff B, Benhamou JP: **Amodiaquine-induced hepatitis. A report of seven cases.** *Ann Intern Med* 1986, **104:**801-3
47. Woodtli W, Vonmoos P, Siegrist P, Zollikofer H: **Amodiaquin-induzierte Hepatitis mit Leukopenie.** *Schweiz Med Wochenschr* 1986, **116:**966-8
48. Charmot G, Goujon C: **Hépatites mineures pouvant êtres dues à l'amodiaquine.** *Bull Soc Pathol Exot* 1987, **80:**266-70
49. Bernuau J, Larrey D, Campillo B, Degott C, Verdier F, Rueff B, Pessayred D, Benhamou JP: **Amodiaquine-induced fulminant hepatitis.** *J Hepatol* 1988, **6:**109-12
50. Raymond JM, Dumas F, Baldit C, Couzigou P, Beraud C, Amouretti M: **Fatal acute hepatitis due to amodiaquine.** *J Clin Gastroenterol* 1989, **11:**602-3
51. Munera Y, Hughes FC, Le Jeunne C, Pays JF: **Interaction of thyroxine sodium with antimalarial drugs.** *BMJ* 1997, **314:**1593
52. McGregor AM: **The thyroid gland and disorders of thyroid function.** *In: Oxford Textbook of Medicine* 1996, 1603-18
53. Barlow JW, Crowe TC, Topliss DJ: **Thyroid hormone antagonism.** *In: Pharmacotherapeutics of the Thyroid Gland.* 1997, 319-42
54. Stroev EA, Kochukov MY, Nikolaev VV: **The lysosomal proteolytic system and functional activity of the rat thyroid in chloroquine administration.** *Eksp Klin Farmakol* 1997, **60:**50-2
55. Smith HR, Croft AM, Black MM: **Dermatological adverse effects with the antimalarial drug mefloquine: a review of 74 published case reports.** *Clin Exp Derm* 1999, **24:**249-54
56. Ashby D, Smyth RL, Brown PJ: **Statistical issues in pharmacoepidemiological case-control studies.** *Statist Med* 1998, **17:**1839-50
57. Boudreau E, Schuster B, Sanchez J, Novakowski W, Johnson R, Redmond D, Hanson R, Dausel L: **Tolerability of prophylactic Lariam® regimens.** *Trop Med Parasitol* 1993, **44:**257-65
58. Petersen E: **Malariaprofylakse. Virkninger og bivirkninger af farmaka der bruges til forebyggelse af malaria.** *Ugeskr Læger* 1997, **159:**2723-30
59. Olsen VV: **Principielle overvejelser vedrørende malariaprofylakse.** *Ugeskr Læger* 1998, **160:**2410-1
60. Ragan E, Wilson R, Li F, Spasoff R, Bigelow G, Spinner N: **Psychotic symptoms in volunteers serving overseas.** *Lancet* 1985, **ii:**37
61. Potasman I, Berry A, Seligmann H: **Neuropsychiatric problems in 2,500 long-term young travellers to the tropics.** *J Travel Med* 2000, **7:**5-9
62. Folkerts H, Kuhs H: **Psychotische Episode infolge Malariaprophylaxe mit Mefloquin: eine kasuistische Mitteilung.** *Nervenarzt* 1996, **63:**300-2
63. Grupp D, Rauber A, Fröscher W: **Neuropsychiatrische störungen nach malariaprophylaxe mit mefloquin.** *Akt Neurol* 1994, **21:**134-6
64. Rønn AM, Bygbjerg IC: **Akut hjernesyndrom efter meflokinbehandling.** *Ugeskr Læger* 1994, **156:**6044-5
65. Hollweg M: **Mefloquininduzierte Psychosen – Probleme der Kausalzuordnung anhand zweier kasuistischer Berichte.** *Psychiatr Prax* 1995, **22:**33-6
66. Heeringa M, Kuster JAM, Meyboom RHB, Bouvy M: **Convulsies tijdens profylactisch gebruik van mefloquine.** *Ned Tijdschr Geneeskd* 1998, **142:**2477-80
67. Jensen JB, Meflochin : **De neuropsykiatriske bivirkninger er ofte alvorlige og kan persistere længe efter ophør med medicinen.** *Ugeskr Læger* 1998, **160:**241
68. Bygberg IC, Rønn AM: **Langvarige neuropsykiatriske bivirkninger efter meflochinprofylakse.** *Ugeskr Læger* 1999, **161:**1422-3
69. Fusetti M, Eibenstein A, Corridore V, Hueck S, Chiti-Batelli S: **Meflochina ed ototossicità: descrizione di tre casi.** *Clin Ter* 1999, **150:**379-82
70. Lysack JT, Lysack CL, Kvern BL: **A severe adverse reaction to mefloquine and chloroquine prophylaxis.** *Aust Fam Physician* 1998, **27:**1119-20
71. Van den Ende J, Coppens G, Verstraeten T, van Haegenborgh T, Depraetere K, van Gompel A, van den Enden E, Clerinx J, Colebunders R, Peetermans WE, *et al*: **Recurrence of blackwater fever: triggering of relapses by different antimalarials.** *Trop Med Int Health* 1998, **3:**632-9
72. Durrheim DN, Gammon S, Waner S, Braack LEO: **Antimalarial prophylaxis – use and adverse events in visitors to the Kruger National Park.** *S Afr Med J* 1999, **89:**170-5
73. Mangalvedhekar SS, Gogtay NJ, Wagh VR, *et al*: **Convulsions in non-epileptics due to mefloquine-fluoroquinolone co-administration.** *Natl Med J India* 2000, **13:**47
74. Nosten F, van Vugt M, Price R, Luxemburger C, Thway KL, Brockman A, McGready R, ter Kuile F, Looareesuwan S, White NJ: **Effects of artesunate-mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: a prospective study.** *Lancet* 2000, **356:**297-302
75. Merritt JC: **Mefloquine not first choice for aircrew.** *BMJ* 1994, **308:**721-2
76. Heno P: **À propos de plongées et tropiques.** *Med Trop* 2000, **60:**103
77. Perry IC: **Malaria prophylaxis.** *BMJ* 1995, **310:**1673
78. Botella de Maglia J, Casanovas AE: **Acerca de la profilaxis del paludismo.** *Rev Clin Esp* 1998, **199:**549-50
79. Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC: **Long-term prophylaxis with weekly mefloquine.** *Lancet* 1993, **341:**848-51

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