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The Mefloquine Drug Issue

Bonnie Toews presents: Since 1992, Canadian, British and American ground forces have been subjected to an antimalarial drug called Mefloquine (Lariam) in deployments to malaria-infested areas such as Somalia, Rwanda, Iraq and Afghanistan. Some soldiers have committed suicide; others have murdered members of their own families while in psychotic states caused by Mefloquine. For too long, coalition forces have denied the devastating side effects this antimalarial drug has on their troops.

Advocates Against Anti-Malara Drug Mefloquine (Lariam)

Mefloquine Link to Suicide Questioned in Parliament
Canada's MP John Cummings Parliamentary History
Dr. Remington Nevin, Major, U.S. Army

Research results on Mefloquine by Army Dr. Remington Nevin

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FRIDAY, SEPTEMBER 17, 2010

New Press Report on Another Mefloquine Victim

Adam Kuligowski says his son and soldiers in his unit were never told about the side effects of the antimalaria drug, Mefloquine. It was issued to Adam and troops like Aspirin in a doggie bag as they boarded the plane to Afghanistan. All of them were told they would be punished if they neglected to take the prescription. U.S. Army NCOs were not told about adverse effects of Mefloquine so they didn't recognize clear signs of trouble prior to his suicide. Father says no one is listening and whole companies of troops are still being issued to Mefloquine as they are deployed to Afghanistan now.
Father talks about his son's struggles with adverse effects of Mefloquine received while on active duty.

Posted by Bonnie Toews at 9:02 AM No comments:

SUNDAY, AUGUST 1, 2010

Mefloquine (Lariam) linked to liver and thyroid damage

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

Ashley M Croft1 and Andrew Herxheimer2
1Surgeon General's Department, Ministry of Defence, St Giles' Court, London WC2H 8LD, UK
2UK Cochrane Centre, NHS R&D Programme, Oxford OX2 7LG, UK
Corresponding author.

Ashley M Croft: AshleyCroft@compuserve.com; Andrew Herxheimer:

Andrew_Herxheimer@compuserve.com

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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, (but many people taking mefloquine may not know they have pre-existing liver or thyroid conditions) 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.

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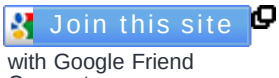

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About Me

BONNIE TOEWS

In 2000, my husband was diagnosed with Parkinson's Disease. He had prematurely aged, had shrunk from his full six-foot stature and refused to take my hand when walking together. One day, hearing his feet shuffling behind mine, I knew in my gut that something was terribly wrong. Because his mother and his grandmother before her were bedridden with Parkinson's, I already suspected Wally had inherited the disease, but it would be five more years before the medical community acknowledged inherited Parkinson's exists. Three studies dealt with three families where Parkinson's had occurred from generation to generation. The researchers discovered through DNA testing that not only did the families carry the Parkinson's gene, they also carried a marker unique to each family. This meant that those who inherit Parkinson's may suffer the most severe form of the disease along with associated components connected to the marker that identify other neurological and movement disorder diseases. Now my husband wants me to share our experience so that other caregivers can prepare for the road ahead of them. For my PROFESSIONAL BIO see http://www.bonnietoews.com

View my complete profile

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 neuropsychiatric 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.

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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).

Table 1

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

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 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]

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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 (T3), and normal free thyroxine (T4) 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 T3, resulting in thyroid hormone antagonism.[53] In the rat, chloroquine injections more than halve the T3 concentration, without changing the level of free T4.[54] Chloroquine has been reported to inhibit T3 uptake in mammalian cells by inhibiting receptor-mediated endocytosis. [53]

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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.

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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.

Posted by Bonnie Toews at 7:49 PM 2 comments:

SUNDAY, JANUARY 18, 2009

Report of the Somalia Commission Inquiry

INQUIRY REPORT SUMMARY

Mefloquine is a relatively new anti-malarial drug, first made generally available to the Canadian public in 1993. It is used both to prevent malaria (that is, as a prophylactic) and to treat malaria. Mefloquine is used in areas where the local strains of malaria have developed a resistance to other anti-malarial drugs. Somalia is one such place.

Some suggestion has been made to this Inquiry that Mefloquine caused severe side effects, including abnormal and violent behaviour, among some Canadian Forces (CF) personnel in Somalia. We were not able to explore fully the possible impact of Mefloquine. This would have required additional hearings dedicated specifically to the issue, which time did not permit. However, we report here our general findings about Mefloquine and its possible impact on operations in Somalia.

It is clear that Mefloquine caused some minor problems in Somalia, as might be expected from a review of the medical literature. We learned of several incidents of gastro-intestinal upset, vivid dreams, nightmares referred to by soldiers as “meflomares,” and inability to sleep following the use of this drug. Side effects - or at least the minor side effects, and possibly also the major side effects - appeared to be most pronounced in the 24 to 48 hours after taking Mefloquine.
If Mefloquine did in fact cause or contribute to some of the misbehaviour that is the subject of this Inquiry, CF personnel who were influenced by the drug might be partly or totally excused for their behaviour. However, for reasons described more fully in Chapter 41, we are not able to reach a final conclusion on this issue. We can offer only general observations about the decision to prescribe Mefloquine for personnel deployed to Somalia:

The decision of the Department of National Defence (DND) in 1992 to prescribe Mefloquine for CF personnel deployed to Somalia appears to be consistent with the medical practice at the time. This view is based on medical literature from that time suggesting that Mefloquine was an appropriate anti-malarial drug for troops in Somalia and that severe neuropsychiatric symptoms were rare - in the order of one in 10,000 to one in 13,000. U.S. troops also used Mefloquine, although in a weaker

form. We cannot say, however, whether DND took adequate precautions to ensure that persons susceptible to severe psychiatric disorders did not receive Mefloquine, since even in 1992 it was known that Mefloquine should not be prescribed to such individuals.

At the time of the deployment, there seems to have been no strong evidence that Mefloquine might interact with alcohol to produce or increase the risk of abnormal behaviour or to magnify such behaviour. The possible adverse effects of mixing alcohol with Mefloquine were analyzed in detail in the medical literature only after the Somalia deployment. DND, therefore, cannot be faulted for failing to relate the consumption of alcohol to the use of Mefloquine.

More recent medical information suggests that severe adverse effects from Mefloquine used as a prophylactic are not as rare as first thought, but views on this point conflict, and further investigation may be necessary.

Mefloquine use could have been a factor in the abnormal behaviour of some troops in Somalia. However, one cannot begin to determine whether Mefloquine contributed to the behaviour of the individuals in question without answers to the following questions:

1. Did the members in question use Mefloquine?

2. Did any of the members in question receive a more powerful 'treatment' dose of Mefloquine? This would happen only if they had contracted malaria. The more powerful treatment doses were known even at the time of the Somalia deployment to carry a greater risk of neuropsychiatric disorders than the weaker dose that most troops received to prevent malaria.

3. Did any of the members in question have a history of psychiatric disorders that could increase the risk of severe side effects from Mefloquine?

4. What day of the week did they take Mefloquine? What day or days of the week did their misbehaviour occur?

5. Did they complain at any point about any symptoms, mild or severe, that are now known to be associated with Mefloquine?

6. Did anyone notice abnormal behaviour by the members in question in the few days after the latter consumed Mefloquine? If so, what was the behaviour?

7. Is it reasonable to say that Mefloquine was or may have been a cause? Might some other factor instead have caused or contributed to the behaviour (alcohol consumption, racist attitudes, generally belligerent or aggressive nature of the individual, stressful environment, official tolerance of extreme behaviour)?

It is evident that further investigation is warranted before any firm conclusions about the role of Mefloquine can be drawn.

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Posted by Bonnie Toews at 1:05 PM 1 comment:

Chemical Make-up of Mefloquine (Larium®)

Drug Category: Antimalarials

Indication: For the treatment of mild to moderate acute malaria caused by Mefloquineuine-susceptible strains of Plasmodium falciparum (both chloroquine-susceptible and resistant strains) or by Plasmodium vivax. Also for the prophylaxis of Plasmodium falciparum and Plasmodium vivax malaria infections, including prophylaxis of chloroquine-resistant strains of Plasmodium falciparum.

Pharmacology: Mefloquine is an antimalarial agent which acts as a blood schizonticide. Mefloquine is active against the erythrocytic stages of Plasmodium species. However, the drug has no effect against the exoerythrocytic (hepatic) stages of the parasite. Mefloquine is effective against malaria parasites resistant to chloroquine. Mefloquine is a chiral molecule. According to some research, the (+) enantiomer is more effective in treating malaria, and the (-) enantiomer specifically binds to adenosine receptors in the central nervous system, which may explain some of its psychotropic effects.

Mechanism of Action: Mefloquine has been found to produce swelling of the Plasmodium falciparum food vacuoles. It may act by forming toxic complexes with free heme that damage membranes and interact with other plasmodial components.

Absorption: Well absorbed from the gastrointestinal tract. The presence of food significantly enhances the rate and extent of absorption.

Toxicity: Oral, rat: LD50 = 880 mg/kg. Symptoms of overdose include nausea, vomiting, and weight loss.

Protein Binding: 98%

Biotransformation: Hepatic. Two metabolites have been identified in humans. The main metabolite, 2,8-bis-trifluoromethyl-4-quinoline carboxylic acid, is inactive against Plasmodium falciparum. The second metabolite, an alcohol, is present in minute quantities.

Half Life: 2-4 weeks

Contraindication: Use of Lariam is contraindicated in patients with a known hypersensitivity to Mefloquineuine or related compounds (eg, quinine and quinidine) or to any of the excipients contained in the formulation. Lariam should not be prescribed for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders, or with a history of convulsions.

Interaction: Drug-drug interactions with Mefloquine have not been explored in detail. There is one report of cardiopulmonary arrest, with full recovery, in a patient who was taking a beta blocker (propranolol). The effects of Mefloquineuine on the compromised cardiovascular system have not been evaluated. The benefits of Mefloquine therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine must not be given simultaneously with or subsequent to Mefloquine.Concomitant administration of Mefloquine and

other related compounds (eg, quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and increase the risk of convulsions. If these drugs are to be used in the initial treatment of severe malaria, Mefloquine administration should be delayed at least 12 hours after the last dose. There is evidence that the use of halofantrine after Mefloquineuine causes a significant lengthening of the QTc interval. Clinically significant QTc prolongation has not been found with Mefloquineuine alone.

This appears to be the only clinically relevant interaction of this kind with Mefloquine, although theoretically, coadministration of other drugs known to alter cardiac conduction (eg, anti-arrhythmic or beta-adrenergic blocking agents, calcium channel blockers, antihistamines or H1-blocking agents, tricyclic antidepressants and phenothiazines) might also contribute to a prolongation of the QTc interval. There are no data that conclusively establish whether the concomitant administration of Mefloquineuine and the above listed agents has an effect on cardiac function.

In patients taking an anticonvulsant (eg, valproic acid, carbamazepine, phenobarbital or phenytoin), the concomitant use of Mefloquine may reduce seizure control by lowering the plasma levels of the anticonvulsant. Therefore, patients concurrently taking antiseizure medication and Mefloquine should have the blood level of their antiseizure medication monitored and the dosage adjusted appropriately.When Mefloquine is taken concurrently with oral live typhoid vaccines, attenuation of immunization cannot be excluded. Vaccinations with attenuated live bacteria should therefore be completed at least 3 days before the first dose of Mefloquine.

No other drug interactions are known. Nevertheless, the effects of Mefloquine on travelers receiving comedication, particularly diabetics or patients using anticoagulants, should be checked before departure.In clinical trials, the concomitant administration of sulfadoxine and pyrimethamine did not alter the adverse reaction profile.

Drug Interaction

Acenocoumarol--Mefloquine can increase the anticoagulant effect
Anisindione--Mefloquine can increase the anticoagulant effect
Dicumarol--Mefloquine can increase the anticoagulant effect
Halofantrine--Increased risk of cardiac toxicity
Rifampin--Rifampin lowers mefloquine levels
Ritonavir--Mefloquine decreases the effect of ritonavir
Warfarin--Mefloquine can increase the anticoagulant effect
Ziprasidone--Increased risk of cardiotoxicity and arrhythmias

Food Interaction:

1. Avoid alcohol.
2. Take with a full glass of water.
3. Take with food.

This project is supported by Genome Alberta & Genome Canada, a not-for-profit organization that is leading Canada's national genomics strategy with $600 million in funding from the federal government. This project is also supported in part by GenomeQuest, Inc., an enterprise genomic information company serving the life science community.

DrugBank Version: 2.5 —

Contact: Craig Knox or Genome Canada Help Desk

Posted by Bonnie Toews at 12:56 PM No comments:

The Full Report on Meqfloquine

Mefloquine

From Wikipedia, the free encyclopedia

Mefloquine is an orally-administered antimalarial drug used as a prophylaxis against and treatment for malaria. It also goes by the trade name Lariam (manufactured by Roche Pharmaceuticals) and chemical name Mefloquine hydrochloride (formulated with HCl). Mefloquine was developed in the 1970s at the Walter Reed Army Institute of Research in the U.S. as a synthetic analogue of quinine.

Mefloquine

Systematic (IUPAC) name
2,8-bis(trifluoromethyl)quinolin-4-yl]-(2-piperidyl)methanol
Identifiers
CAS number
53230-10-7
ATC code
P01BC02
PubChem
4046
DrugBank
APRD00300
Chemical data
Formula
C17H16F6N2O
Mol. mass
378.312 g/mol
Pharmacokinetic data
Bioavailability
?
Metabolism
Extensively hepatic; main metabolite is inactive
Half life
2 to 4 weeks
Excretion
Primarily bile and feces; urine (9% as unchanged drug, 4% as primary metabolite
Therapeutic considerations
Pregnancy cat.
C (U.S.)
Legal status

Routes
oral

Contents

Uses

Mefloquine is used to prevent malaria (malaria prophylaxis) and also in the treatment of chloroquine-resistant falciparum malaria. As Mefloquine resistance spreads, Mefloquine has started to lose its efficacy.
Mefloquine is the drug of choice to treat malaria (though not necessarily to prevent malaria) caused by chloroquine-resistant Plasmodium vivax.[1]
Mefloquine has shown efficacy in an in vitro assay against Progressive Multifocal Encephalopathy (PML). Biogen Idec has recently announced that a trial of Mefloquine in HIV-related PML is beginning.[1]

Side Effects

Mefloquine may have severe and permanent adverse side effects. It is known to cause severe depression, anxiety, paranoia, aggression, nightmares, insomnia, seizures, birth defects, peripheral motor-sensory neuropathy,[2] vestibular (balance) damage and central nervous system problems. For a complete list of adverse physical and psychological effects — including suicidal ideation — see the most recent product information. Central nervous system events occur in up to 25% of people taking Lariam, such as dizziness, headache, insomnia, and vivid dreams. In 2002 the word "suicide" was added to the official product label, though proof of causation has not been established. Since 2003, the Food and Drug Administration (FDA) in the USA has required that patients be screened before Mefloquine is prescribed. The latest Consumer Medication Guide to Lariam has more complete information.

Attempting to obtain a diagnosis of Mefloquine toxicity is frustrated by the following reasons:
1. It may cause bad dreams.
2. In most cases, results from the primary tools used by neurologists - CAT scans, EMGs and MRIs - come up negative.
3. Thousands of travelers do take Mefloquine every year, however the adverse reaction data is spurious and under-reported because side-effects occur usually in a location away from the doctor that originally prescribed the drug.
4. Because the data is spurious and under-reported, reports of Mefloquine reactions are readily discounted as "anecdotal," since Mefloquine toxicity is not as well-known and publicly acceptable as, for example, an allergic reaction to Penicillin.

In the 1990s, there were reports in the media[3] that the drug may have played a role in the Somalia Affair, which involved the torture and murder of a Somali citizen whilst in the custody of Canadian peacekeeping troops. There has been similar controversy, since three murder-suicides involving Special Forces soldiers at Fort Bragg, N.C., in the summer of 2002. To date, more than 19 cases of vestibular damage following the use of Mefloquine have been diagnosed by military physicians. The same damage has been diagnosed among business travelers and tourists.

Neurological Activity

In 2004, researchers found that Mefloquine in adult mice blocks connexins called Cx36 and Cx50.[4] Cx36 is found in the brain and Cx50 is located in the eye lens. Connexins in the brain are believed to play a role in movement, vision and memory, likely due to a role in the synchronization of neural activity.

Chirality and Its Implications

Mefloquine is a chiral molecule with two asymmetric carbon centers, which means it has four different diastereomers. The drug is currently

manufactured and sold as a racemate of the (+/-) R*,S* enantiomers by Hoffman-LaRoche, a Swiss pharmaceutical company. According to some research,[5] the (+) enantiomer is more effective in treating malaria, and the (-) enantiomer specifically binds to adenosine receptors in the central nervous system, which may explain some of its psychotropic effects. It is not known whether Mefloquine goes through stereoisomeric switching in vivo.

The (+) enantiomer has a shorter half-life than the (-) enantiomer.
Recent peer-reviewed research findings from
Walter Reed Army Institute of Research (WRAIR)
Mefloquine was invented at WRAIR in the 1970s. WRAIR has published several papers outlining their efforts to make Mefloquine safer by producing a version of Mefloquine that is composed of only the (+) enantiomer (photo isomer).

“Adverse central nervous system (CNS) events have been associated with Mefloquine use. Severe CNS events requiring hospitalization (e.g., seizures and hallucinations) occur in 1:10,000 patients taking Mefloquinefor chemoprophylaxis. However, milder CNS events (e.g., dizziness, headache, insomnia, and vivid dreams) are more frequently observed, occurring in up to 25% of patients.”[6]

WRAIR defines the neurotoxicity of Mefloquine to be 25 µM from table 1 ref.[6] “We recently showed that Mefloquine severely disrupts calcium homeostasis in rat neurons in vitro at concentrations in excess of 20 µM, an effect closely related to the acute neurotoxicity of the drug in terms of dose effect and kinetics.”[6]

“However, the drug crosses the blood-brain barrier and accumulates as much as 30-fold in the central nervous system, and Mefloquine brain concentrations as high as 50 µM have been reported in human postmortem cases. Mefloquine brain concentrations as high as 90 µM have been reported in rats given a therapy-equivalent dose rate, with concentrations in subcompartments in the brain exceeding 100 µM. Since it has long been known that a prolonged disruption of neuronal calcium homeostasis may lead to neuronal cell death and injury, it is reasonable to suppose that such events may contribute to the clinical neuropathy of the drug.”[6]

In addition, WRAIR published the following in March 2006 regarding treatment-level brain-stem damage in rats:
It states:
1. “At the time this study was conceived, no formal FDA guidelines for neurotoxicity testing existed. In contrast, first-tier neurological screens, such as those recommended by the U.S. Environmental Protection Agency (EPA), are often employed to detect a broad range of possible neurological effects that may be induced by uncharacterized test compounds.”[7]
The FDA “approval” process in 1970 did not require safety testing for neurotoxicity, since no protocol existed at the time. Evidence suggests that it still does not exist, since the Walter Reed researchers had to use a test protocol from the EPA to write this paper.
2. “It is also important to point out that the Mefloquine-induced brain-stem injury revealed by silver staining is permanent in nature.”[7]
Proposed development of a commercially available safety test
WRAIR recently released a funding document STTR A06-T034 “Neurotoxicity Associated with Mefloquine, an Anti-Malarial Drug.”[8]
This document calls for the development of a commercially-available “safety test” for Mefloquine users.

Popular Culture References

The fictional drug "Quinium," which has significant similarities to Mefloquine, was featured in the episode "Goliath" of the television series Law and Order: SVU.[9]

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Further Reading

Phillips-Howard, P. A., and F. O. ter Kuile. 1995. CNS adverse events associated with antimalarial agents: fact or fiction? Drug Saf. a370-383.

External Links

Manufacturer's information page
Lariam Action USA, Clearinghouse for information on Mefloquine news, research, toxicity
2004 UPI story about military suicides
Senator Feinstein Urges Rumsfeld to Complete Lariam Study.
Discussion of Lariam side-effects at PeaceCorpsOnline.org

Posted by Bonnie Toews at 12:45 PM No comments:

Beware Antimalarial Drug, Mefloquine--still being issued to troops

In 1994, the president of my publishing company assigned me to cover the humanitarian relief effort following the Rwandan genocide. My article became a tribute to the overlooked logistics industry for its part in making such efforts the success they are, but I also stepped into the mire of the antimalaria drug scandal.

Cpl. Scott Smith, a peacekeeper I interviewed, later committed suicide on Christmas Eve, 1994, in Rwanda—two months before his tour of duty was up. He was coming home to a fantastic job, and in my interviews

and regular talks with him, I was impressed with his upbeat, resourceful attitude. I have dealt with despondent people and know their skill for covering depression. Scott showed none of the signs, but he did talk about the terrible nightmares and diarrhea he was having especially on the days the troops took their weekly Mefloquine pill. He had endured these side effects in deployments to the Gulf War and Somalia as well. (You start taking the pill one week in advance of visiting a tropical area and for four weeks following your return.)

For this assignment, the cameraman and I were also issued Mefloquine (Lariam®). When flying on the armed forces transports delivering supplies to the refugee camps in Goma, Zaire, the pilots joked about not being on Mefloquine because "you can't have pilots hallucinating in the air."

According to a report from the National Defence Department in Ottawa for the Somalia Enquiry, "some Canadian Forces pilots and divers received another anti-malarial drug, Doxycycline, because Mefloquine was thought to cause dizziness and loss of fine motor control in some users. The post-deployment report of the HMCS Preserver, for example, stated that all aircrew on active flying duties used Doxycycline. The report also noted that several CF members who suffered adverse effects from taking Mefloquine were switched to Doxycycline."

The peacekeepers described the designated day their companies took Mefloquine as *Manic Monday*, *Loco Tuesday*, *Wacky Wednesday*, *Psycho Thursday* or *Freaky Friday*. On these days, military stats show the rate of vehicle accidents rose. There are now medical papers available describing the dangers of mixing alcohol with Mefloquine, and Scott was naturally drinking on that Christmas Eve in celebration of his going home soon. He loved being in Rwanda and helping the people who were so appreciative of the Canadians who stayed behind and risked their lives to bring world attention to the genocide being executed in Rwanda at a rate much higher and more efficiently than any organized genocide previously committed, even by the Nazis.

I was only on Mefloquine nine weeks, but just that short time created a state of insomnia that began in Rwanda and lasted six months until sleep deprivation weakened my immune system and I collapsed with pneumonia. Then I was heavily drugged so I could sleep. Fourteen years later, I am lucky if I get five hours solid sleep per night, and for seven years, my thyroid had to be monitored because it showed strange scar-like damage. I constantly fluctuated between hyper- and hypothyroidism, so doctors were never sure what treatment course to take. Instead of doing the wrong thing, they decided to monitor it every three months. Somehow, on my own, my thyroid finally corrected itself and is now working normally. Was it Mefloquine? Others who have taken this drug have suffered serious damage to their livers, hearts and/or thyroids and haven't healed themselves.

The military in the U.S., Britain, Canada and Australia have minimized the dangers of Mefloquine since the U.S. Army asked Roche Labs to create a shot that would prevent soldiers from being infected with one form of malaria they could not treat, and as a result those infected with it often died. Today, the number of troops suffering from the devastating adverse effects from taking Mefloquine far outweighs the danger of any of them dying from this form of malaria.Yet, U.S. and Canadian forces—probably British and Australian and all coalition forces too, but I don't have confirmation of that—have issued Mefloquine in Iraq (but have since stopped) and continue to issue it in Afghanistan,

despite reported evidence from the Gulf War, Angola relief effort, Somalia and Haiti UN Missions and Rwandan mission, plus other tropical deployments, that a significant number of troops are suffering from debilitating side effects, including suicides and/or aggressive violent behavior that has ended up in murder, usually of family members and, for sure, of spouses.

SOLDIERS FOR THE TRUTH talk about it on their web site. The Canadian National Defence Department finally issued a paper discussing the adverse effects in 1995, but the public didn't know about it. CTV broadcaster, Christine Neilsen, produced an investigative report on W5 in October 1997. She took the plea of the suicide soldier's mother seriously to investigate his death because she too had suffered adverse effects from taking Mefloquine on an assignment to Angola. She proved that the Canadian peacekeepers were being used as unwitting guinea pigs for the drug and suggested the true culprit in the Somalia scandal was Mefloquine, which affected the soldiers' behavior and emotional states. Her research assistant uncovered the signed documents between Health Canada, the Department of National Defence and the drug company. Did the Canadian people rise up in revolt as a result of this scandalous treatment of our armed forces? No, Parliament barely uttered a peep.

We say we support our armed forces, but no one puts the brakes on issuing a drug that decimates our forces faster and more viciously than armed conflict. A British Medical Report sites the number as high as 1 in 10 people suffer adverse effects. They have been observing the results because, of all Western nations, a high proportion of British travelers visit tropical countries where malaria occurs. Canada admits that 1 in 1,000 can be adversely affected. Israel estimates 1 in 100,000. Whatever the ratio really is, it is TOO HIGH. We charge our armed forces with the job of saving our butts, but we don't raise a finger to protect them from a drug company that has expanded its production of Mefloquine from the States to Pakistan under a different name, and this subsidiary has yet to place adequate warnings on its label to prescription users. NOT ACCEPTABLE.

USER BEWARE:

DOCTOR MICHELLE BRILL-EDWARDS, Canadian drug safety expert from transcript of radio interview with CBC's Jennifer Westaway, August 26, 2002, 9:45 a.m., Reference NO. 226387-7:

BRILL-EDWARDS: "Well firstly, I should mention that there's a spectrum of what you could... as lay people understand this affects on the brain, or neuro-psychiatric side effects. Some of these are very common, every day problems that are not so severe, things like disturbed sleep, terrible dreams and so forth. But the more severe end of that spectrum of effects on the brain are actual psychosis, what we call acute psychosis, which, in lay terms, would be going crazy, someone who is out of touch with reality and whose actions can be bizarre. In particular, a big concern had been unexplained feelings of suicide and homicide."

BRILL-EDWARDS: "Usually, there's a very strict order to not use this drug with alcohol. And the U.S. military has a good track record of trying to keep their military men dry in the field of battle. But once they return home, of course, then that restriction is off and alcohol may become a question. And we know that the drug lasts for a very long time in the body and this mixture may be lethal."

BRILL-EDWARDS: "There is one study done by the military that was a carefully-done study that watched military men taking the drug in the field and they were seen weekly. And it's a very interesting point that in that study, two men had to be

withdrawn from the study because of suicidal ideation."

WESTAWAY: "What military was this?"

BRILL-EDWARDS: "This was the American military. And interestingly, of the 203 - I think it was - men in the study who had Mefloquine doses use in prophylaxis, two developed suicidal ideation. That would suggest that we're dealing with a serious psychiatric side-effect rate that is in the order of one in 100, not one in 12,000. . . . It changes the whole balance of whether and when this drug should be used in comparison with other drugs."

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Posted by Bonnie Toews at 12:17 PM 1 comment:

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