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## Mefloquine use, psychosis, and violence: A retinoid toxicity hypothesis

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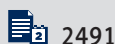
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Mefloquine use has been linked to severe gastrointestinal and neuropsychiatric adverse effects, including cognitive disturbances, anxiety, depression, psychosis, and violence. The adverse effects of the drug are thought to result from the secondary consequences of hepatocellular injury; in fact, mefloquine is known to cause a transient, anicteric chemical hepatitis. However, the mechanism of mefloquine-associated liver damage and the associated neuropsychiatric and behavioral effects of the drug are not well understood. Mefloquine and other 8-amino-quinolines are the only antimalarial drugs that target the liver-stage malaria parasites, which selectively absorb vitamin A from the host. Vitamin A is also stored mainly in the liver, in potentially poisonous concentrations. These observations suggest that both the therapeutic effectiveness of mefloquine and its adverse effects are related to the ability of the 8-aminoquinolines to alter the metabolism of retinoids (vitamin A and its congeners). Several lines of evidence support the hypothesis that mefloquine neurotoxicity and other adverse effects reflect an endogenous form of hypervitaminosis A due to a process involving: mefloquine-induced dehydrogenase inhibition; the accumulation of retinoids in the liver; retinoid-induced hepatocellular damage; the spillage of stored retinoids into the circulation; and the transport of these compounds to the gut and brain in toxic concentrations. The retinoid hypothesis could be tested clinically by comparing cases of mefloquine toxicity and untreated controls in terms of retinoid profiles (retinol, retinyl esters, percent retinyl esters, and retinoic acid). Subject to such tests, retinoid profiling could provide an indicator for assessing mefloquine-associated adverse effects.

**Key words:** mefloquine • neurotoxicity • liver • retinoids • depression • psychosis • violence

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## Background

Mefloquine (Lariam), a synthetic quinoline introduced in the late 1970s for the prevention and treatment of malaria, has been linked to a wide range of adverse cardiovascular, gastrointestinal, and neuropsychiatric effects. Of particular concern are reports of an association between mefloquine use and severe anxiety and depression, cognitive disturbances and, more worryingly, psychosis and violence [1,2]. Mefloquine prophylaxis has been implicated in numerous impulsive suicides and homicides, including deaths in military personnel [3]. After 2002, as a result of such incidents, a history of neuropsychiatric disorder was designated a contraindication for prescribing mefloquine by the U.S. Army. A study carried out in 2007 on a cohort of 11,725 active duty U.S. military personnel showed that 38.4% had received a prescription for mefloquine in the 45 days prior to combat deployment. A review of records showed that 1127 (9.6%) of the entire cohort had contraindications to mefloquine use. Yet 155 persons – 13.8% of those with contraindications and 1.3% of the entire cohort – had been prescribed mefloquine. Thus, 1 in 7 individuals with neuropsychiatric contraindications had received a prescription for mefloquine prior to a recent combat deployment. Since mefloquine continues to be used as an antimalarial, further research is recommended on the incidence and mechanisms of mefloquine-associated adverse events [4].

In a study of the effects of mefloquine on brain function, Hood et al. [5] found that mefloquine caused a concentration-dependent decrease in glutathione and a simultaneous increase in F(2)-isoprostanes in primary rat cortical neurons, indicating the presence of oxidative stress. Mefloquine also induced a concentration-dependent decrease in the number of spines per neuron and spine density, suggesting that oxidative stress caused by the drug was associated with synaptodendritic degeneration. The molecular mechanisms of mefloquine-induced oxidative stress on brain function and behavior remain uncertain. This paper presents the hypothesis that mefloquine toxicity is an endogenous form of hypervitaminosis A induced by liver damage and the subsequent spillage and transport of stored retinoids in toxic concentration to the brain, gut, and other affected tissues.

## Quinolones and Malaria Prophylaxis

The quinolones, including chloroquine, primaquine, mefloquine and quinine, are among the most successful yet poorly understood classes of drugs, with important uses in the treatment of systemic lupus erythematosus and HIV as well as malaria. The 8-amino-quinolines in particular (mefloquine, primaquine, and tafenoquine) are the only drugs that target the liver-stage (merozoite) malaria parasites [6]. Malarial infection begins when a person is bitten by an infected female

anopheles mosquito and *Plasmodium* parasites are injected into the bloodstream in the form of sporozoites, which travel to the liver. After 7–10 days, during which there are no symptoms, the parasites emerge from the liver cells as merozoites and enter the bloodstream, where they invade and multiply in erythrocytes. When the cells burst, the parasites invade more erythrocytes. Clinical symptoms occur in synchrony with the rupture of infected erythrocytes [7].

Potential clues to understanding both the therapeutic effectiveness of mefloquine and its adverse effects are that the *Plasmodium falciparum* parasite selectively absorbs vitamin A from the host [8] and appears to use the vitamin for its metabolism [9]. Persons with low vitamin A reserves are at increased risk of death from malaria, whereas those with high reserves have less severe disease and are less likely to die from it [10]. Although therapeutically weaker than currently available antimalarial drugs such as artemisinin derivatives, vitamin A has a beneficial adjunctive role in the treatment of malaria and partially protects against malaria infection [11–13]. The selective absorption of vitamin A by the malaria parasite suggests that the effectiveness and toxicity of mefloquine are due in part to the ability of the 8-aminoquinolines to alter the metabolism of vitamin A and its congeners (collectively termed retinoids). As discussed below, there are indications that mefloquine interferes with retinoid metabolism via its effect on dehydrogenase enzymes in the liver.

## Retinoids

Retinoids are fat-signaling molecules derived mainly from the diet. They are stored principally (about 80% of total vitamin) in the liver, particularly in the stellate cells, and in sufficient quantity to last the average adult about 2 years without additional intake. In normal physiological concentrations, retinoids are essential for multiple biologic functions, including cellular homeostasis, embryonic development, tissue differentiation and growth, and mucus secretion [14,15]. Retinoic acid (RA), the major active form of vitamin A, binds to and activates specific retinoid receptors that regulate the transcription of many target genes [16]. RA is produced from free retinol in a process that involves the hydrolysis of retinyl esters in the liver, the release of retinol into the circulation, and its subsequent delivery to the target tissues bound to retinol-binding protein (RBP). Retinoic acid is synthesized from the oxidation of retinol to retinaldehyde via an alcohol dehydrogenase, and from retinaldehyde via an aldehyde dehydrogenase reaction [17].

The importance of vitamin A for the nutrition of the parasite suggests that the antimalarial effect of mefloquine could be due to interference with retinoid metabolism by acting as a dehydrogenase inhibitor. This hypothesis is supported by a

study in which a functional proteomic approach was used to exploit the structural similarity between quinolones and the purine ring on ATP to identify quinoline-binding proteins. Two human proteins were identified: aldehyde dehydrogenase 1 (ALDH1) and quinine reductase 2 (QR2), and both were found to be selectively inhibited by quinolones. Another inhibitor of ALDH1 (dimethylaminobenzaldehyde) was also lethal to or inhibited the growth of *P. falciparum* *in vitro* but was less effective in killing the parasites than the quinoline compounds themselves [18]. Chloroquine actively accumulates to millimolar concentrations in the skin and eye when administered at therapeutic levels, and one of the functions of ALDH1 in the eye is to catalyze the conversion of retinaldehyde to retinoic acid [18]. Prolonged use of chloroquine or hydroxychloroquine could therefore cause retinopathy and blindness due to the accumulation of retinaldehyde in the retina [19]. In an earlier related study, mefloquine increased protein degradation but impaired the breakdown of lipids in rat liver lysosomes, resulting in the accumulation of lipids in lysosomes [20].

## Mefloquine, Liver Damage, and Retinoids

Mefloquine is an effective drug for the prophylaxis and treatment of malaria caused by *P. falciparum*. Although generally well tolerated with few adverse effects, the drug is known to cause a transient, anicteric chemical hepatitis, with slightly elevated liver enzymes, indicating hepatocellular damage [21]. A review of 516 cases suggested that many of the adverse effects of mefloquine are a post-hepatic syndrome caused by primary liver damage, with symptoms that include malaise, fever, anorexia, headache, abdominal pain, nausea, diarrhea, and concentration difficulties [22]. However, the precise mechanisms linking mefloquine-associated liver damage with neurotoxicity are not well understood.

The hypothesis proposed here is that the action of mefloquine as a dehydrogenase inhibitor leads to the accumulation of retinoids in the liver, resulting in inflammatory changes and subclinical hepatitis. This is followed by the spillage and regurgitation of stored retinoids into the circulation in toxic concentrations and their subsequent transport to the gut and brain, where they induce the adverse gastrointestinal and neuropsychiatric adverse effects of the drug as manifestations of an endogenous form of hypervitaminosis A. The effectiveness of the drug against malaria may be similarly due to hepatic retinoid accumulation and exposure of the merozoite-stage parasites to retinoid concentrations that exceed their tolerance threshold and result in their destruction. Evidence in support for this hypothesis is presented below.

As noted, retinoids are stored in high concentration in the liver, mainly in the form of retinyl esters, and they are normally

secreted harmlessly into the circulation as RBP. However, retinyl esters can be extremely toxic if released unbound to protein. An accepted indicator of retinoid toxicity is percent retinyl esters >10% of total vitamin A [23,24]. Liver damage is a known result of excess vitamin A exposure and is associated with reduced serum retinol level but increased liver enzyme levels [25]. Retinoid-induced hepatotoxicity leads to a form of cholestatic liver dysfunction in which bile regurgitates into the circulation, raising the level of all biliary substances in the blood [26,27]. Vitamin A metabolites in bile acids also spill over into the circulation, while stored retinyl esters leak from damaged hepatocytes [28] in proportion to the total liver stores of the vitamin [29]. At the same time, plasma retinol levels decline due to impaired hepatic synthesis and mobilization of the vitamin. The hypothesized net effect is an endogenous form of hypervitaminosis A associated with an increased percentage of plasma retinyl esters as a fraction of total vitamin A, together with increased retinoic acid (RA) concentrations and low or normal concentrations of retinol and its transporter, RBP.

## Retinoid Toxicity, Brain and Behavior

The postulated link between mefloquine-induced liver dysfunction and subsequent neuropsychiatric adverse effects due to the spillage of toxic concentrations of retinoids into the circulation receives strong support in the literature. Retinoid signaling pathways affect the functioning of the adult brain via retinal dehydrogenases, cellular retinoid binding proteins, and retinoid receptors, and are essential for cognitive and behavioral development. Furthermore, many neuronal genes are responsive to retinoids, suggesting that retinoid-responsive gene transcription has a significant impact on adult brain function. At normal physiological concentrations in the brain, RA acts as a growth factor, participates in locomotor behavior, and modulates dopaminergic pathways and cells [30]. In the functional cerebral cortex, RA signaling affects the expression and regulation of hundreds of genes through the retinoic acid receptor (RAR) and retinoid X receptor (RXR) classes of ligand-dependent transcription factors, influencing the pattern formation of many organs and tissues [31]. Increased concentrations of RA are found in the adult brain in the striatum and the nucleus accumbens. Retinaldehyde dehydrogenase 1 (RALDH1) is present in the dopaminergic terminals that innervate the striatum from the ventral tegmental area and are necessary for the synthesis of RA in these areas. RA modulates the action of dopamine by regulating the D2 receptor [32].

In higher concentrations, however, retinoids inhibit cell growth and can be pro-oxidant, cytotoxic, mutagenic, and teratogenic. Acute vitamin A toxicity is characterized by nausea, vomiting, headache, vertigo, blurred vision, increased intracranial

pressure, irritability, and muscular incoordination. Vitamin A toxicity can occur due to excessive dietary consumption and from treatment with retinoids, as well as endogenously due to medical conditions related to, for example, altered liver and kidney function [24].

Reports have also suggested an association between the use of 13-cis-RA (or isotretinoin), a medication for acne, and the onset of depression, as well as psychosis and suicide in a subgroup of vulnerable individuals [33,34]. This evidence includes case reports, studies showing a temporal association between depression onset and exposure to the drug, challenge and re-challenge cases, evidence of a drug class effect, dose response, and the existence of biologically plausible mechanisms for the association [35–37]. Therapeutic doses reportedly induce cognitive disturbances and depression in from 1% to 11% of patients [38].

Studies in mice also show that 13-cis-RA adversely affects learning and memory and significantly increases depression-like behaviors [39,40]. Recalling the study of Hood et al. [5], which showed that mefloquine induces oxidative stress on brain function, other reports suggest that acute and chronic vitamin supplementation of laboratory animals at therapeutic doses also leads to increased levels of markers of oxidative stress in liver mitochondria and substantia nigra, and to alterations in locomotor and exploratory activity [41]. Vitamin A supplementation at clinical doses also impairs mitochondrial function in rat hippocampus, decreases brain-derived neurotrophic factor levels and dopamine D2 receptor levels, and decreases glutamate uptake [42].

### Similarities Between Vitamin A Poisoning and Impulsive Violence

Hypervitaminosis A was unwittingly induced in early Arctic explorers by consuming vitamin A-rich polar bear or seal liver. Reported symptoms included drowsiness, irritability, severe headaches, nausea, and various forms of impulsive and irrational behavior called *pibloktoq* by the Eskimos [43]. Unlike the sympathetic nervous system-based “fight-or-flight” response, in which the senses are heightened, cognitive functions are at their sharpest and the skeletal muscles primed for decisive action, the arousal state associated with hypervitaminosis A is more akin to one of intoxication. Reports of incidents of impulsive violence suggest similarities to those induced by hypervitaminosis A. Such accounts describe violent acts as being carried out in a state of diffuse cognitive impairment, perceptual distortion and anhedonia, and in a dream-like state from which the subject later emerges with little or no memory of the acts in question [44–46].

In addition to causing neuropsychiatric symptoms such as depression, psychosis, and violence, synthetic retinoids in particular have also been linked to a wide range of adverse and often severe gastrointestinal effects [47]. For instance, in a large case-control study involving thousands of patients with Crohn’s disease (CD) and ulcerative colitis (UC), it was found that UC was strongly associated with previous isotretinoin exposure (odds ratio (OR) 4.36, 95% confidence interval (CI): 1.97, 9.66) but not with CD (OR 0.68, 95% CI: 0.28, 1.68). Moreover, increasing the dose of isotretinoin was associated with elevated risk of UC, and the risk of UC was highest in those exposed to isotretinoin for more than 2 months (OR 5.63, 95% CI: 2.10, 15.03) [48]. This evidence suggests that both the adverse neuropsychiatric and gastrointestinal effects of mefloquine may be mediated by retinoid overexpression and toxicity.

### Conclusions

The use of mefloquine in the prevention and treatment of malaria has been increasingly linked to a broad range of neuropsychiatric effects, including depression, psychosis, and violence. Mefloquine is known to cause a transient, anicteric chemical hepatitis and the adverse effects of the drug have been postulated to result from the secondary consequences of hepatocellular injury. However, the precise mechanisms linking mefloquine-induced liver damage and the adverse neuropsychiatric effects are not well understood. The explanation for both the therapeutic effectiveness of mefloquine and its adverse consequences may lie in its ability to interfere with the hepatic metabolism of retinol, possibly via dehydrogenase inhibition. This would be expected to cause retinyl esters to accumulate to high concentrations in the liver and also to destroy the merozoite-stage malaria parasites *in situ*. Thus, mefloquine and other 8-amino quinolones may cause liver damage in susceptible persons due to the accumulation of retinoids, which are known to be potentially hepatotoxic. The symptoms of mefloquine toxicity may result from the spillage of stored retinoids from the damaged liver into the circulation and their transport to the gut and brain, causing the adverse neuropsychiatric and gastrointestinal symptoms as a function of an endogenous form of hypervitaminosis A. Indeed, evidence has been presented in this paper that supports this hypothesis. The retinoid hypothesis could be tested clinically by comparing cases of mefloquine toxicity and untreated controls in terms of retinoid profiles (retinol, retinyl esters, percent retinyl esters, and retinoic acid). Cases would be expected to have a significantly increased percentage of plasma retinyl esters as a fraction of total vitamin A, as well as increased retinoic acid (RA) concentrations and low or normal concentrations of retinol and its transporter, RBP. Subject to the outcomes of such tests, retinoid profiling could provide an indicator for assessing mefloquine-associated adverse effects.

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