Mefloquine Decreases Immobility In the Tail Suspension Test

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Introduction
Mefloquine hydrochloride (MFQ) is a 4-methanoloquinoline anti-malarial drug in a class known as Hemozoin inhibitors. MFQ is one of the most widely used malaria prophylaxis available, as it has demonstrated efficacy even against strains of Plasmodium species which are multi-drug resistant.

However, MFQ’s efficacy comes with a robust side effect profile, which includes anxiety, depression, unusual behavior, and suicidal ideation, as well as increasing susceptibility to pneumonia, and cardiac abnormalities.

MFQ’s psychotropic effects are of particular concern due to their use by the military in combat zones where malaria is present. MFQ use has been suspected of contributing to violent incidents among soldiers in Somalia, Iraq, and Afghanistan, leading the military to reconsider its use, though it remains in use to this day.

MFQ is currently sold as the racemate of its enantiomers, and research appears to indicate that the (+) enantiomer is more effective at treating malaria, whereas the (-) enantiomer has an affinity for adenosine receptors and is thought to be responsible for the more severe side effects.

The Tail Suspension test
The tail suspension test is a commonly employed behavior assay of the effects of antidepressant drugs. The test is short-lasting (6 minutes), simple to conduct, and considered less aversive than the forced swim-test, an older test of depressive behavior.

This test involves suspending the mouse by the tip of its tail from a rod or cable with front paws off the ground. Across the course of the six minute period, energetic struggling is eventually replaced with periods of increased immobility, not because of fatigue but rather because of the inescapable nature of the task.

Drugs/manipulations that decrease the amount of time spent immobile are those that also tend to be effective in treating depression in human subjects.

To determine effects of MFQ in the short- and long-term, our lab has undertaken a number of tests of its effects. In this exploratory pilot study we attempted to determine the short-term effects of a short (4-day) daily regimen of MFQ. We hypothesized that repeated doses of MFQ would lead to persistent neuro-chemical changes that altered levels of immobility in this task.

Methods
Subjects were 32 mice, strain C57BL/6J (females, approximately 20-30 g weight) bred in house using stock from Jackson Laboratories). Subjects were maintained on a reversed 12:12 light-dark schedule with no food or water restrictions, and were handled for a number of days before the test.

During the exposure period, subjects were given 4 days of exposure to a regimen of MFQ (25 mg/kg in corn oil vehicle, 1 injection/day, n=15) or vehicle alone (n=19). At the end of this period subjects were removed to their home cages for a drug-free period of two days.

At the end of this period, subjects were tested - affixed by the tip of the tail to a raised plastic rod so that the mouse was suspended a few centimeters above the ground. The subject was removed from the bar after 6 minutes. Behavior was recorded via videotape, and the total amount of time spent immobile (out of 360 seconds total) was scored by an observer blinded to experimental conditions. One mouse (MFQ group) was incorrectly suspended and cut from data analysis.

Results
Time Spent Immobile

![Figure 1: Graph showing time spent immobile over different conditions](image)

**Figure 1** shows the time spent immobile over different conditions.

**Discussion**
Our results show that the effect of the MFQ regimen was to decrease mobility in the tail suspension test. This suggests that use of this drug may have stimulatory effects, perhaps even pushing users in the direction of a manic state.

One possible mechanism by which MFQ might have this effect is through its effects on adenosine. Like caffeine, MFQ is an adenosine antagonist and may produce stimulatory effects through that route. However, unlike caffeine, MFQ has a half-life measured in weeks (2-4 weeks) rather than hours.

Persistent stimulatory effects (over the course of weeks and perhaps even months, since MFQ is administered weekly for anti-malarial prophylaxis) that acutely manifest in an anti-depressive/manic effect might ultimately result in sleep disruption, fatigue, and depression over time.

It is conceivable that MFQ given to soldiers already undergoing wartime stress could create new and/or exacerbate existing psychiatric problems, increasing the likelihood of anxiety, depression, and stress-related disorders.

Future Directions
Future studies in our lab are underway examining the effect of MFQ days and weeks after administration. It is possible that what begins as a stimulatory effect (tested 48 hours after the end of the 4-day regimen) would ultimately result in a depressive state as continually stimulation interferes with sleep and potentiates stress-related physiological responses. We are also exploring the possibility of examining MFQ effects on sleep patterns. In addition, the stimulatory short-term effect seen here might also increase anxiety levels in the short term; tests of anxiety (such as the light-dark box or elevated t-maze) might also reveal effects of MFQ.

![Tail Suspension Test Figure](image)