Mefloquine toxicity: implications for serving personnel and veterans of the Australian Defence Force.

Dr Jane C. Quinn

A Submission to the Senate Foreign Affairs, Defence and Trade References Committee Inquiry into the Mental Health of Australian Defence Force Serving Personnel.

Background

The synthetic quinoline derivative mefloquine is a highly effective anti-malarial, but the drug is now also recognized as a potent neurotoxicant that, much like lead or mercury, may cause permanent injury to the central nervous system [1]. First synthesised in the late 1960's, mefloquine was developed as part of a U.S. military drug discovery programme that was mounted to identify novel antimalarial compounds in response to concerns of rising chloroquine resistance, particularly in the theatres of operation in South East Asia [2-7]. Soon after its initial synthesis, mefloquine was expeditiously developed by the pharmaceutical company F.Hoffmann-La Roche[8, 9], and released to the commercial market in the 1980's after limited clinical testing [10, 11].

Mefloquine was subsequently widely advocated as the drug of choice for travellers to areas known to be endemic for chloroquine-resistant malaria [12] such as sub-Saharan Africa and South-East Asia [13, 14] and became the first line of defence against malaria for the U.S and U.K. militaries, and the second line of defence for the Australian Defence Force. During this time, it was reported to be 'well tolerated, safe, and effective' [15] despite coincident reports of severe neuropsychiatric side effects in isolated cases [16].

Despite these early claims of safety, an increasing body of evidence has established that potentially serious symptoms of central nervous system drug toxicity, referred to as "side effects" by the manufacturer, occur far more commonly that had been previously recognized. The current Australian mefloquine product data sheet notes that "very common" reactions affecting greater than 10% of users include "abnormal dreams" and "insomnia". "Common" reactions affecting between 1-10% of users include "anxiety", "depression", "visual impairment", and "vertigo"[17]. Reactions described as "uncommon" but nonetheless affecting between 1 and 10 users per 1000 include "agitation, restlessness, mood swings, panic attacks, confusional state, hallucinations, aggression, bipolar disorder, psychotic disorder including delusional disorder, depersonalization and mania, paranoia, suicidal ideation", as well as "memory impairment", and "long term" vestibular disorders[17].

To acknowledge the potential for lasting adverse reactions, in 2013, the U.S. drug regulator, the Food and Drug Administration, required that the mefloquine product label include a boxed warning, or "black box", warning that "[m]efloquine may cause neuropsychiatric adverse reactions that can persist after mefloquine has been discontinued". The FDA also required the mefloquine documentation to include the warning that "[d]izziness, vertigo, tinnitus, and loss of balance can go on for months or years after mefloquine is stopped or may become permanent" [18] and the following warning concerning psychiatric adverse reactions:

> "Psychiatric symptoms ranging from anxiety, paranoia, and depression to hallucinations and psychotic behavior can occur with mefloquine use. Symptoms may occur early in the course of mefloquine use. In some cases, these symptoms have been reported to continue for months or years after mefloquine has been stopped. Cases of suicidal ideation and suicide have been reported"

Ever since the drug was first marketed in the U.S., mefloquine product documentation has warned that the onset of certain psychiatric symptoms that may occur early during the course of mefloquine use must be considered "prodromal", or as an early warning sign, of "more serious" drug toxicity. To reflect this, the current U.S. mefloquine product documentation clearly states clearly that:

> "During prophylactic use, the occurrence of psychiatric symptoms such as acute anxiety, depression, restlessness or confusion suggest a risk for more serious psychiatric disturbances or neurologic adverse reactions. In these cases, the drug should be discontinued…"

The U.S. "black box" warning expands on this guidance to note that "During prophylactic use, if psychiatric or neurologic symptoms occur, the drug ***should*** be discontinued…" (emphasis added)[19]. The current Australian warning further notes that "if signs of unexplained acute anxiety, depression, restlessness or confusion are noticed… [i]n these cases, ***the drug must be discontinued****"* (emphasis added) [17].

It is therefore of critical importance that troops administered mefloquine on deployment are made explicitly aware of the range of potential neurological and psychiatric reactions they may experience when taking mefloquine — including seemingly benign but potentially significant reactions such as abnormal dreams and insomnia —and of the need to report these symptoms as soon as possible to medical authorities so that the guidance that "the drug should be discontinued" or that "the drug must be discontinued" may be properly considered.

A military culture which is dismissive of mental health concerns, or the use of mefloquine on deployments where such psychiatric symptoms may already be common or perceived as normal, increases that likelihood that personnel may fail to report such adverse reactions, or that medical authorities will fail to recognize them as evidence of drug toxicity. Failing to report such adverse reactions increases the risk that personnel will continue taking the drug despite clear warnings from the manufacturer and drug regulators that, in such cases, the drug "should" or "must" be discontinued. In addition, some of the "prodromal" symptoms, such as confusion [20], can have severe detrimental effects on the ability of the affected individual to effectively report these side effects, further compounding this problem.

Together, these issues indicate the importance of accurate recording of all prescription medications issued to service personnel both prior to or within deployment phases, in order to easily identify those that have been exposed to mefloquine (or other quinoline derivates) for malarial prophylaxis, and appropriate post-prescription mental health monitoring in order to detect, and intervene, when symptoms arise. With a heavy reliance on self-reporting, and limited post deployment psychological monitoring, there is significant scope for those suffering from adverse effects of exposure to mefloquine to remain unidentified in the system. As the symptoms of mefloquine toxicity can both abate, but also increase in intensity over time, it cannot be assumed that post-operational psychological screening at 3 and 6 months is sufficient to identify all of those affected.

Although the syndrome of mefloquine toxicity, a collection of significant neurological and psychiatric symptoms affecting balance, vision, hearing, memory, mood, and behaviour, has been formally described in the literature [21, 22], the military has been slow to accept mefloquine toxicity as a possible diagnosis when individuals present with complex neurological and psychiatric issues, and where mefloquine exposure can be identified in their medical history. The reason for this is unclear but a lack of recognition of this syndrome is likely to be contributing to poorer mental health outcomes for military personnel affected by this disorder.

Accurate diagnosis of mefloquine toxicity is also critical to prevent a confounding diagnosis of Post Traumatic Stress Disorder (PTSD) in service personnel. Although the two conditions are not mutually exclusive, it is possible to be suffering from both PTSD and mefloquine toxicity concurrently, a diagnosis of mefloquine toxicity can have significant implications for the treatment of symptoms common to both disorders. In a document discussing special medical considerations required when treating (US) military personnel for malarial prophylaxis on deployment, The Centre for Disease Control and Prevention in the USA has noted that exposure to mefloquine may 'confound the diagnosis and management' of PTSD[23]. The presentation of permanent neurological damage, including vertigo, balance disorders and visual disturbance including photophobia, in the absence of a severe initiating traumatic incident, can aid in distinguishing between the two syndromes, providing evidence of exposure is also present[21].

Failure of appropriate diagnosis can also have more serious consequences. What is currently known of the underlying pathophysiology of mefloquine toxicity means that the efficacy of commonly used neuropsychiatric drugs for treatment of affected personnel is unclear, and currently no studies been undertaken to identify best possible therapeutics for treatment of either the acute or chronic neurological or psychiatric symptoms. This presents the possibility that treatment of affected individuals with psychiatric medications could result in an exacerbation of symptoms with significant detrimental health effects.

In Conclusion:

A correct diagnosis mefloquine toxicity, in cases where neurological symptoms are present and mefloquine exposure can be confirmed, is critical to determine appropriate and effective treatment. It is possible to identify symptoms associated with mefloquine toxicity that are not usually present in other 'common' psychological or neurological syndromes experienced by military personnel. Given the issues with reporting, and the potentially confounding diagnosis of PTSD, identification and review of all ADF personnel exposed to mefloquine during their active service should be undertaken with some urgency. Misdiagnosis of mefloquine toxicity as PTSD, or PTSD without taking into account the potential confounding effects of mefloquine toxicity, could result in long-term treatment mismanagement of affected individuals, potentially exacerbating their symptoms rather than relieving them. Therefore, it is critical that the neurotoxic syndrome caused by mefloquine exposure is recognised by military medical professionals and that this diagnosis be taken into account when considering treatment options for military personnel affected by mental health disorders in the ADF.

References

1. Dow, G., et al., *Mefloquine induces dose-related neurological effects in a rat model.* Antimicrob Agents Chemother, 2006. **50**(3): p. 1045-53.
2. Berliner, R.W., Butler, T.C., *Summary of data on the drugs tested in man.* A survey of Antimalarial Drugs, 1941-1945. Vol. 1. 1946, Ann Arbor, MI.: Edwards Brothers.
3. Tigertt, W.D., *Army Malaria Research Program.* Annals of Internal Medicine, 1969. **70**(1): p. 150-&.
4. Schmidt, L.H., et al., *Antimalarial activities of various 4-quinolonemethanols with special attention to WR-142,490 (mefloquine).* Antimicrob Agents Chemother, 1978. **13**(6): p. 1011-30.
5. Coatney, G.R., *Pitfalls in a Discovery - Chronicle of Chloroquine.* American Journal of Tropical Medicine and Hygiene, 1963. **12**(2): p. 121-&.
6. Tigertt, W.D., *Present and Potential Malaria Problem.* Military Medicine, 1966. **131**(9S): p. 853-&.
7. Shookhof.Hb, et al., *Chloroquine-Resistant Falciparum Malaria.* Journal of the American Medical Association, 1967. **202**(10): p. 989-&.
8. Maugh, T.H., *Malaria - Resurgence in Research Brightens Prospects.* Science, 1977. **196**(4288): p. 413-&.
9. Maugh, T.H., *Malaria Drugs - New Ones Are Available, but Little Used.* Science, 1977. **196**(4288): p. 415-415.
10. Trenholme, C.M., et al., *Mefloquine (WR 142,490) in the treatment of human malaria.* Science, 1975. **190**(4216): p. 792-4.
11. Rieckmann, K.H., et al., *Prophylactic Activity of Mefloquine Hydrochloride (Wr 142490) in Drug-Resistant Malaria.* Bulletin of the World Health Organization, 1974. **51**(4): p. 375-377.
12. Hall, A.P., *The treatment of malaria.* Br Med J, 1976. **1**(6005): p. 323-8.
13. Bhattacharya, D.N. and A.P. Hall, *Chloroquine-resistant falciparum malaria from East Africa.* J Trop Med Hyg, 1986. **89**(6): p. 291-4.
14. Chabasse, D., et al., *Chloroquine-resistant Plasmodium falciparum in Mali revealed by congenital malaria.* Trans R Soc Trop Med Hyg, 1988. **82**(4): p. 547.
15. Bulletin, W., *Development of mefloquine as an antimalarial drug. UNDP/World Bank/WHO update,* in *Bull World Health Organ*. 1983. p. 169-78.
16. Harinasuta, T., D. Bunnag, and W.H. Wernsdorfer, *A phase II clinical trial of mefloquine in patients with chloroquine-resistant falciparum malaria in Thailand.* Bull World Health Organ, 1983. **61**(2): p. 299-305.
17. La-Roche, F.H., *Product information leaflet. PIL.4158,* in *Roche Producst Pty Ltd*. 2014, Roche Producst Pty Ltd: Dee Why, Australia.
18. Agency, U.S.F.a.D.A., *FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects,* U.S.F.a.D.A. Agency, Editor. 2013.
19. Agency, F.D.A., *Product label information - mefloquine hydrochloride.* 2013.
20. Javorsky, D.J., et al., *Cognitive and neuropsychiatric side effects of mefloquine.* J Neuropsychiatry Clin Neurosci, 2001. **13**(2): p. 302.
21. Nevin, R.L., *Mefloquine and posttraumatic stress disorder.*, in *Textbook of military medicine. Forensic and ethical issues in military behavioural health.*, E.C. Ritchie, Editor. 2015, Borden Institute: Washington D.C. p. 277-296.
22. Nevin, R.L., Ritchie, E.C., *The mefloquine intoxication syndrome: A significant potential confounder in the diagnosis and management of PTSD and other chronic deployment-related neuropsychiatric disorders.*, in *Post-Traumatic Stress Disorder and Related Diseases in Combat Veterans. (In press).* 2016, Springer International: Switzerland.
23. McGill, A.J., *Chapter 8. Special Considerations for US military deployments.*, in *The Yellow Book: CDC health information for internation travel.*, G.W. Brunette, Editor. 2016, Oxford University Press.