Mefloquine as a prophylaxis for malaria needs to be revisited

Sundus Shafat Ahmad a, Manju Rahi b, Vikash Ranjan a, Amit Sharma a,c, *  

a ICMR-National Institute of Malaria Research, New Delhi, India  
b Indian Council of Medical Research, New Delhi, India  
c International Centre of Genetic Engineering and Biotechnology, New Delhi, India

A B S T R A C T

According to WHO, 2019 witnessed 229 million cases of malaria globally, of which Africa accounted for 94% of cases. Early diagnosis and treatment are the basis of malaria management, and the need for good chemoprophylaxis especially for people travelling to endemic areas is vital. There are a number of drug options available for the prophylaxis of malaria, mefloquine being one of the drugs used. Mefloquine has been around from the 1970s, and was developed in the United States keeping in mind the soldiers that were being deployed to areas where chloroquine resistant strains of Plasmodium were discovered. Mefloquine was preferred for its once a week dosage. Within a decade of its introduction, reports of the side effects associated with its long-term use surfaced. Mefloquine is now reported to cause a myriad of neuropsychiatric side effects including anxiety, sleep disturbance, depression, dizziness and frank psychosis, especially in patients with pre-existing psychiatric disorders. Many countries like the United States and the United Kingdom have updated their drug boxes to include the warning of these potential neuropsychiatric effects. This paper reviews the side effects of mefloquine and why there is a need to revisit its use in Indian drug policy.

Malaria continues to be a public health problem in India. Estimates by World Health Organization in 2019 (WHO) reported 229 million cases in comparison to 251 million in 2010 and 231 million in 2017 (World Malaria Report 2020). The African Region shouldered the largest burden with estimated 213 million cases (94%) whereas the South-East Asia Region reported 3% and the rest of the world accounted for 3% (World Malaria Report 2020). Almost 95% of all malaria cases globally in 2019 were in 29 countries, of which India reported the largest absolute reductions in cases over a decade i.e., 20 million cases in 2000 to 5.6 million in 2019 (World Malaria Report 2020).

Early diagnosis and timely treatment are the mainstay of malaria management and the chemoprevention of malaria is an important aspect. The need of chemoprophylaxis arises when people travel to malarious areas and desire protection against this potentially life-threatening infection, more so in susceptible populations. People travel for various reasons and travel has exponentially increased in recent times. Hence antimalarial prophylaxis is needed. International bodies like the World Health Organization (WHO: International Travel and Health, Chapter 7) and the Centre of Disease Control and Prevention (CDC Yellow Book 2020) recommend atovaquone-proguanil, doxycycline, chloroquine, mefloquine or tafenoquine (details listed in Table 1) as prophylactics for both short and long-term travelers. The drug list remains the same but special attention has to be paid to side effects if drug is taken for more than 6 months (WHO: International Travel and Health, Chapter 7).

Malaria prevention in armed forces, especially those deployed to endemic areas and forest areas (Ranjha and Sharma, 2021) is especially crucial. According to CDC guidelines (CDC Yellow Book 2020) in military population of USA, atovaquone-proguanil is the choice of prophylaxis for a short- and long-term deployments in high-transmission geographical areas. Those who are unable to take atovaquone-proguanil due to intolerance or contraindication, the second line prophylactic is doxycycline, followed by mefloquine. Prior to prescribing mefloquine for prophylaxis, absolute and relative contraindications are taken into consideration (HA Policy 2015). On the other hand, as per National Drug Policy on Malaria (2013) of India chemoprophylaxis is recommended in specific groups in P. falciparum malaria endemic areas. For short term travelers with stay of less than 6 weeks, daily dose of 100 mg of doxycycline is the drug of choice in adults, starting 2 days before travel to 4 weeks after departure. For a duration of more than 6 weeks, mefloquine chemoprophylaxis should be administered weekly, starting 2 weeks before travel to 4 weeks after departure (National Drug Policy on
which is mefloquine. In this paper, we focus on prophylaxis by mefloquine, its related side effects and an appropriate alternative.

In the 1970s, the development of mefloquine was initiated by Walter Reed Army Institute of Research (WRAIR), USA, owing to emergence of chloroquine resistance in P. falciparum malaria in Southeast Asia (WHO and F. Hoffmann-La Roche, 1991). The drug was tested in clinical trials on prisoners and soldiers, and people in developing countries. In an extensive review by WHO, in late 1980s and early 1990s, after the licensing and introduction of mefloquine, it became extensively used for chemoprophylaxis. Over 20 million people consumed mefloquine as it was preferred for its weekly-single dose (WHO and F. Hoffmann-La Roche, 1991). Despite the lack of clinical safety and tolerability phase III data in civilian volunteers, initial license was granted (Croft, 2007) and numerous trials have been conducted since then.

Mefloquine, [2,8-bis(trifluoromethyl)quinolin-4-yl]-piperidin-2-ylmethanol is a 4-quinolinemethanol antimalarial and antiparasitic which acts as a blood schizonticide, structurally related to quinine. Since its development it is indicated for both prophylaxis and treatment of malaria, despite the inadequately understood mechanism of action (Taylor and White, 2004). A long half-life of 13–30 days provides an edge over other prophylactics as it can be used in a once-a-week format in lower doses (WHO and F. Hoffmann-La Roche, 1991).

### Table 1

| Drug       | Frequency | When to start before travel | When to stop after travel | Contraindications                                      |
|------------|-----------|-------------------------------|---------------------------|-------------------------------------------------------|
| Atovaquone | Daily     | 1–2 days                      | 1 week (Unless any dose is missed during travel, 4 weeks) | Renal impairment                                      |
| Proguanil  | Weekly    | >2 weeks                      | 4 weeks                   | CQ and MQ resistance                                  |
| Chloroquine| Weekly    | 1–2 weeks                     | 4 weeks                   | Risk of photosensitivity                              |
| Doxycycline| Daily     | 1–2 days                      | 4 weeks                   | Areas of MQ resistance                                |
| Mefloquine | Weekly    | >2 weeks                      | 4 weeks                   | Psychiatric conditions, seizure disorder, cardiac conduction abnormalities |
| Primaquine | Daily     | 1–2 days                      | 1 week                    | Renal impairment, photosensitivity                    |

#### 2. Possible mechanisms of neurotoxicity

The gastrointestinal side effects of mefloquine are known to be caused by pancreatic β-cell type-KATP channel Kir6.2/SUR1 inhibition. The mechanism behind these neurological and psychiatric effects is not completely known but the mechanisms implicated include: cholinesterases inhibition, non-receptor tyrosine kinase 2 (Pyk2 and/or interaction with adenosine A (2A) receptors (Lee et al., 2017). Some studies have also shown mefloquine to cause GABAergic interneuron dysfunction, inhibition of cellular transport and depression of cortical activity (Martin et al., 2021).

Studies have focused on the role of mefloquine in causing hallucinations, nightmares and a flare up of symptoms of Post-Traumatic Stress Disorder (PTSD) (Janowsky et al., 2014). The detrimental effects mefloquine can produce, have the potential to continue even after drug is stopped leading to long-term neurotoxic effects (Quinn, 2015). Experiences in Armed Forces and civilian populations in different countries (summarized in Table 2) have highlighted the significance of taking mefloquine’s adverse effects in cognizance.

On the 29th of July 2013, the FDA issued a Drug Safety Communication, reinforcing the updated warnings regarding these side effects of mefloquine and adding a black boxed warning to the drug label. The medication guide has also been revised by the FDA to include these side effects and that these may be persistent or become permanent. Since the FDA warning, drug regulatory agencies in various countries, including the UK, Ireland (Nevin and Byrd, 2016), and Canada (Nevin, 2017) have made it mandatory to add a warnings update in their mefloquine drug labels.

### 3. The Indian context

**National Drug Policy on Malaria (2013) of India** envisaged mefloquine use as chemoprophylaxis when stay in a malarious region is for more than 6 weeks. This policy has implications for the general public but especially so for armed forces personnel who are posted in malarious areas where they are exposed to risks of contracting malaria. Generally, chemoprophylaxis for malaria is prescribed only in certain groups and in areas with high prevalence of P. falciparum. In addition to vector control products, for longer stays chemoprophylaxis is required. Armed personnel who are posted in malaria endemic regions for long-term are at high risk of infection and as per guidelines mefloquine is recommended for periods above 6 weeks. However, to our knowledge there are no reports pertaining to neuropsychiatric side effects till date in context of Indian troops, this may be due to lack of systematic studies.
Table 2
Results of studies pertaining to mefloquine prophylaxis safety.

| Year | Study                      | Country         | Participants | Result: % of participants suffering adverse effects | Result: % of participants suffering neuropsychiatric adverse effects |
|------|----------------------------|-----------------|--------------|-----------------------------------------------------|------------------------------------------------------------------|
| 1993 | Boudreau et al.            | US              | 203          | 43%                                                 | Not determined                                                   |
| 1996 | Phillips and Kass          | Australia       | 285          | 51.2%                                               | 6.3%                                                             |
| 1996 | Buma et al.                | Netherlands     | 2289         | 22.8%                                               | Not determined                                                   |
| 1996 | Schlenzenne et al.         | Switzerland     | 420          | 11.2%                                               | 7.9%                                                             |
| 1996 | Croft and World            | UK              | 317          | 29%                                                 | Not determined                                                   |
| 1999 | Peragallo et al.           | Italy           | 1386         | 17%                                                 | Not determined                                                   |
| 2001 | Overbosch et al.           | Netherlands, Germany, UK, Canada and SA | 483 | 42% | 29% |
| 2005 | Kirschner et al.           | Australia       | 1157         | 57%                                                 | 29%                                                              |
| 2005 | Vaillancourt et al.        | Canada          | 1413         | 74.7%                                               | Not determined                                                   |
| 2007 | Fujii et al.               | Japan           | 1876         | 24.4%                                               | 18.2%                                                            |
| 2008 | Andersson et al.           | Sweden          | 488          | 57%                                                 | 21.7%                                                            |
| 2010 | Nasveld et al.             | Australia       | 162          | 11.7%                                               | 5%                                                               |
| 2014 | Ringqvist et al.           | Denmark         | 73           | Not determined                                     | 55%                                                              |
| 2014 | Peragallo et al.           | Italy           | 4123         | 21.2%                                               | Not determined                                                   |
| 2016 | Ministry of defence        | UK              | 116704       | Not determined                                     | 10%                                                              |
| 2017 | Eick-Cost et al.           | US              | 367840       | Not determined                                     | 10.8%                                                            |

Further, mefloquine is still used in India in civilian populations as well albeit with warnings.

4. Conclusions

After years of use in international military, many of the risks of using mefloquine have been recognized and now more informed policies are being formulated in many countries. The change in policies is based on evidence generated by scientific studies and clinical experience of adverse side effects especially those of neuropsychiatric nature. Mefloquine still remains indicated for malaria prophylaxis for long-term use. Chemoprophylaxis of malaria can be achieved, especially in chloroquine-resistant P. falciparum regions by other drugs available like doxycycline and atovaquone/proguanil as both are well tolerated for chloroquine-resistant P. falciparum. India has been considering tafenoquine for doxycycline and atovaquone/proguanil as both are well tolerated for chloroquine-resistant P. falciparum. Mefloquine still remains indicated for malaria prophylaxis for long-term use. Further, mefloquine is still used in India in civilian populations as well albeit with warnings.

Authors contributions

AS conceived the idea, VR and SSA did extensive literature reviews. SSA and MR drafted the manuscript. MR made important additions. All authors wrote the paper. All authors read and approved the final manuscript.

Disclaimers

The views expressed in the submitted article are authors’ and not an official position of the institution.

Sources of support

None.

Funding

None.

Data sharing

No additional data.

Ethical approval

Not required.

Declaration of competing interest

None of the authors have any conflicts of interest to declare.

Acknowledgments

We thank Department of Science and Technology (DST) for the JC Bose fellowship to AS.

References

Ahmad, S.S., Babi, M., Sharma, A., 2021. Relapses of Plasmodium vivax malaria threaten disease elimination: time to deploy tafenoquine in India? BMJ Global Health 6 (2), e004558. https://doi.org/10.1136/bmjgh-2020-004558.

Andersson, H., Asling, H.H., Falck, B., et al., 2008. Well-Tolerated chemoprophylaxis uniformly prevented Swedish soldiers from Plasmodium falciparum malaria in Liberia, 2004-2006. Mil. Med. 173, 1194-1198.

Bernard, J., Le, C.J., Sarrouy, J., Renaudineau, J., Geffray, L., Dufour, P., et al., 1987. Toxic encephalopathy caused by mefloquine? Presse Med. 16 (3), 1654e5.

Boudreau, E., Schuster, B., Sanchez, J., et al., 1993. Tolerability of prophylactic Lariam regimens. Trop. Med. Parasitol. 44 (3), 257-265.

Buma, A.P.H., van Thiel, P.P., Lobel, H.O., et al., 1996. Long-term malaria chemoprophylaxis with mefloquine in Dutch marines in Cambodia. J. Infect. Dis. 173 (6), 1506-1509.

Croft, A.M., 2007. A lesson learnt: the rise and fall of Lariam and Halfan. J. R. Soc. Med. 100 (4), 170–174.

Croft, A.M., World, M.J., 1996. Neuropsychiatric reactions with mefloquine chemoprophylaxis. Lancet 347, 326.

Eick-Cost, A.A., Hu, Z., Rohrbeck, P., et al., 2017. Neuropsychiatric outcomes after mefloquine exposure among U.S. military service members. Am. J. Trop. Med. Hyg. 96, 159-166.

Fujii, T., Kaku, K., Jelinek, T., Kimura, M., 2007. Malaria and mefloquine prophylaxis use among ground joint self-defense force personnel deployed in East Timor. J. Trav. Med. 14 (4), 226–232.

International Travel and Health. Chapter 7, Malaria. Available from: https://www.who.int/ith/2017-ith-chapter7.pdf. Accessed on December 20, 2020.

Janovsky, A., et al., 2014. Mefloquine and psychotomimetics share neurotransmitter receptor and transporter interactions in vitro. Psychopharmacology 231 (14), 2771–2783.

Kitchener, S.J., Nasveld, P.E., Gregory, R.M., Edstein, M.D., 2005. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. Med. J. Aust. 182 (4), 168–171.

Lee, S.J., ter Kuile, F.O., Price, R.N., Luxemburger, C., Nosten, F., 2017. Adverse effects of mefloquine for the treatment of uncomplicated malaria in Thailand: a pooled
analysis of 19, 850 individual patients. PLoS One 12 (2), e0168780. https://doi.org/10.1371/journal.pone.0168780.

Martins, A.C., et al., 2021 Mar. Review of the mechanism underlying mefloquine-induced neurotoxicity. Crit. Rev. Toxicol. 51 (3), 209-216.

Mccarthy, S. Malaria prevention, mefloquine neurotoxicity, neuropsychiatric illness, and risk-benefit analysis in the Australian defence force. J. Parasitol. Res. 2015:1-23.

Ministry of Defence, 2016. Uk Armed Forces Prescribed Mefloquine Hydrochloride and Subsequent Presentation to Mod Specialist Mental Health Services, 1 April 2007 – 20 September 2015. Available from: https://www.gov.uk/government/statistics/modnational- and- official- statistics- by- topic. (Accessed 15 December 2020).

Nasveld, P.E., Edstein, M.D., Reid, M., et al., 2010. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob. Agents Chemother. 54 (2), 792-798.

National Drug Policy on Malaria, 2013. Available from: https://nvbdcp.gov.in/index.php. (Accessed 12 December 2020).

Nevin, R.L., Byrd, A.M., 2016. Neuropsychiatric adverse reactions to mefloquine: a systematic comparison of prescribing and patient safety guidance in the US, UK, Ireland, Australia, New Zealand, and Canada. Neurol Ther 5 (1), 69-83. https://doi.org/10.1007/s40120-016-0045-5.

Nevin, R.L., 2017. Implications of changes to the mefloquine product monograph. Can. J. Hosp. Pharm. 70 (4), 323-324. https://doi.org/10.4212/cjhp.v70i4.1687.

Nevin, R.L., 2014. Neurotoxic Vestibulopathy: Antimalarial Drugs that Can Cause Vestibular Dysfunction. Vestibular Disorders Association, Portland, Ore, USA. Available from: http://vestibular.org/sites/default/files/pagefiles/Documents/Mefloquine Neurotoxicity.pdf. (Accessed 15 December 2020).

Overbosch, D., Schilthuis, H., Bienzle, U., et al., 2001; Oct 1. Atovaquone/proguanil Mccarthy, S. Malaria prevention, mefloquine neurotoxicity, neuropsychiatric illness, and risk-benefit analysis in the Australian defence force. J. Parasitol. Res. 2015:1-23. DOI:10.1155/2015/287651. M. A. Phillips and R. B. Kass. User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis. Journal of Travel Medicine.1996;3(1):40-45.

Ministry of Defence, 2016. Uk Armed Forces Prescribed Mefloquine Hydrochloride and Subsequent Presentation to Mod Specialist Mental Health Services, 1 April 2007 – 20 September 2015. Available from: https://www.gov.uk/government/statistics/modnational- and- official- statistics- by- topic. (Accessed 15 December 2020).

Peragallo, M.S., Sabatinelli, G., Sarnicola, G., 1999. Compliance and tolerability of mefloquine and chloroquine plus proguanil for long-term malaria chemoprophylaxis in groups at particular risk (the military). Trans. R. Soc. Trop. Med. Hyg. 93 (1), 73-77.

Peragallo, M.S., Sarnicola, G., Boccolini, D., et al., 2014. Risk assessment and prevention of malaria among Italian troops in Afghanistan, 2002 to 2011. J. Trav. Med. 21, 24-32.

Phillips, M.A., Kass, R.B., 1996. User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis. J. Trav. Med. 3 (1), 40-45.

Phillips, M.A., Kass, R.B., 1996. User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis. J. Trav. Med. 3 (1), 40-45.

Ranjha, R., Sharma, A., 2021. Forest malaria: the prevailing obstacle for malaria control and elimination in India. BMJ Global Health 6 (5), e005391. https://doi.org/10.1136/bmjgh-2021-005391.

Ringqvist, A., Bech, P., Glenthøj, B., Petersen, E., 2014. Acute and long-term psychiatric side effects of mefloquine: a follow-up on Danish adverse event reports. Trav. Med. Infect. Dis. 13 (1), 80-88.

Schlagenhauf, P., Steffen, R., Lobel, H., et al., 1996. Mefloquine tolerability during chemoprophylaxis: focus on adverse event assessments, stereochemistry and compliance. Trop. Med. Int. Health 1 (4), 485-494.

Taylor, W.R., White, N.J., 2004. Antimalarial drug toxicity: a review. Drug Saf. 27 (1), 25-61.

Toovey, S., 2009. Mefloquine neurotoxicity: a literature review. Trav. Med. Infect. Dis. 7 (1), 2-6.

Travel-Related Infectious Diseases- Chapter 4. Yellow Book 2020. CDC. Available from: https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria. Accessed on December 20, 2020.

Vaillancourt, R., Ma, J., Sampalis, J., 2005. Assessment of risks associated with short-term use of mefloquine in Canadian forces members: a descriptive cross-sectional study. Can. Pharm. J. 138 (7), 42.

World Malaria Report 2020. Geneva. Available from: https://www.who.int/publications/i/item/9789240015791. (Accessed 15 December 2020).

World Health Organization, F. Hoffmann-La Roche, 1991. Review of the Central Nervous System Adverse Events Related to the Anti-malarial Drug, Mefloquine (1985–1990). Tech. Rep. WHO/MAL/91.1063. World Health Organization, Geneva, Switzerland. Available from: http://apps.who.int/iris/bitstream/10665/61327/1/WHO MAL 91.1063.pdf.