

# A study on mefloquine-associated neuropsychiatric manifestations among Nepalese soldiers posted for United Nations peace mission

Katuwal N<sup>1</sup>, Khatri D<sup>2</sup>, Shrestha DB<sup>3</sup>, Dhungel O<sup>4</sup>, Oli PR<sup>5</sup>, Aryal BB<sup>5</sup>, Rawal N<sup>1</sup>, Rana KJB<sup>2</sup>, Manandhar P<sup>1</sup>, Panta C<sup>2</sup>

<sup>1</sup>Nagendra Katuwal, Lecturer; Namrata Rawal, Associate Professor; Pradeep Manandhar, Lecturer; Department of Neuropsychiatry, Shree Birendra Hospital, Chhauni; Nepalese Army Institute of Health Sciences (NAIHS). <sup>2</sup>Devendra Khatri, Associate Professor; Kishor JB Rana, Professor; Chiranjibi Panta, Lecturer; Department of Medicine, Shree Birendra Hospital, Chhauni; NAIHS. <sup>3</sup>Dhan Bahadur Shrestha, Medical Officer; Mangalbare Hospital, Uurlabari, Morang, Nepal. <sup>4</sup>Omkar Dhungel, Medical Officer; Shree Birendra Hospital, Chhauni. <sup>5</sup>Prakash Raj Oli & Barun Babu Aryal, Intern; Shree Birendra Hospital, Chhauni.

## Abstract

**Background:** Mefloquine is one of the prophylactic medications recommended by the government of Nepal. In areas of intense malaria transmission, prophylaxis with drugs is an important strategy to prevent malaria. During prophylactic use, several neuro-psychiatric and other systemic adverse effects can occur with mefloquine. Notable psychiatric manifestations include anxiety, depression, restlessness, and confusion.

**Objective:** To study the psychiatric effects of mefloquine in Nepalese serving soldiers posted in the United Nations peace mission nations of the African continent taking mefloquine prophylaxis.

**Methodology:** This prospective descriptive study was conducted among Nepalese soldiers posted for United Nations peace mission in South Sudan over a period of one year. Soldiers of age group 25-55 years posted for peace mission having no past and family history of psychiatric illnesses were enrolled in the study. General Health Questionnaire-12, translated into Nepali by Nepalese Journal of Psychiatry, with a questionnaire about the side effects was used to collect detailed information.

**Results:** A total of 524 soldiers posted on peace mission were enrolled in the present study, among which 520 were male and four were female. There were four positive cases with General Health Questionnaire score 3/12 or more. Among the adverse events noted, neuropsychiatric adverse events were more common than non-neuropsychiatric adverse events but none were of life-threatening severity.

**Conclusion:** In a malaria endemic region with a high prevalence of malaria, mefloquine can be safely used in an apparently healthy population, judging the risk-benefit.

**Key words:** Mefloquine; Nepal army; Neuro-psychiatric manifestation

## INTRODUCTION

The number of soldiers going on United Nations (UN) peacekeeping missions annually is around 10,000 with current deployment 4366, in the different countries allocated by the UN<sup>1</sup>. Malaria is endemic in 109 countries and these countries are visited by more than 125 million

travelers each year. About 10,000 international travelers from non-endemic areas who lack immunity to malaria fall ill with malaria after returning home from travel to malaria-endemic countries<sup>2</sup> and the real figure may be up to 30,000 as they were underdiagnosed, treated aboard or underreporting. About 1-4% of travelers who acquire *P. falciparum* malaria will die. Travelers to sub-Saharan Africa are most at risk of contracting malaria. Recent estimates suggest an attack rate of malaria of 302 in 100,000 travelers to West Africa compared to lower rates in Southern Africa (49/100,000) and much

### Address for correspondence

Dhan Bahadur Shrestha  
Mangalbare Hospital, Uurlabari, Morang, Nepal  
E-mail: medhan75@gmail.com

lower rates in East Asia (5.4/100,000) and the Americas (1/100,000)<sup>3</sup>. In Nepal, there were 1,674 confirmed cases of malaria in 2070/71 B.S, with 585 imported cases. The proportion of *P. falciparum* infections were 13 percent in the reporting year. The total *P. falciparum* cases were 224 and among them, 142 were imported<sup>4</sup>. Most cases of imported malaria are preventable using appropriate chemoprophylaxis, but many travelers fail to use or comply with appropriate chemoprophylaxis<sup>5</sup>. An important factor contributing to this failure is the concern about side effects associated with antimalarial chemoprophylaxis. Along with atovaquone/proguanil and doxycycline, mefloquine is currently recommended as malaria prophylaxis for travel in areas with chloroquine-resistant *Plasmodium falciparum*<sup>6</sup>.

There have been many neuropsychiatric disturbances of mefloquine use reported in the literature since its use in therapy for malaria treatment and prophylaxis. In spite of this, it is in use in several countries as a prophylactic agent these days too<sup>3</sup>. During prophylactic use, the occurrence of psychiatric symptoms such as acute anxiety, depression, restlessness or confusion suggests a risk for more serious psychiatric disturbances or neurologic adverse reactions<sup>6</sup>. Though there are many reports from the all over the world, the neuropsychiatric manifestations among Nepalese soldiers using mefloquine as a prophylactic medication for malaria are unknown.

In order to investigate these effects, this prospective study was conducted on Nepalese serving soldiers posted in UN peace mission nations of the African continent taking mefloquine prophylaxis to observe the psychiatric effects of mefloquine.

## METHODOLOGY

The study was conducted among Nepalese soldiers deployed for UN peace mission in South Sudan. This was a descriptive study conducted over a period of one year from 15<sup>th</sup> Aug 2015 to 15<sup>th</sup> Sept 2016.

**Inclusion criteria:** Nepalese soldiers of age group 25-55 years posted for UN peace mission, confirmed to be taking mefloquine, and having no past and family history of psychiatric illnesses.

**Exclusion criteria:** Soldiers having a past history of neuropsychiatric disorders or a family history of neuropsychiatric disorders, seizure disorder, head injury, excessive alcohol consumption and those below the age of 25 and above the age of 55 years.

General Health Questionnaire-12 (GHQ-12), a validated scale developed to measure mental health<sup>7</sup>. Its translated version from English to Nepali by Nepalese Journal of Psychiatry was used in the study to identify a deviation in mental health among serving soldiers under mefloquine prophylaxis. In addition to GHQ, mefloquine side effect questionnaire (developed by Lariam action; an independent information and support group for people with mefloquine toxicity) was used in an interview to collect detailed information about health condition before, during and after the completion of mefloquine prophylactic regimen. These questionnaires were used by medical officer posted on UN mission (co-author of this study) to collect the data. The GHQ was considered positive if it came with score  $\geq 3/12$ . Among positive cases, further detailed inquiry was made to dig down the problem patient was having, using a side effect questionnaire to get the systemic symptomatology.

During that time period, the subjects were informed about the nature of the study and informed consent was obtained. They were asked about their previous illness, any family history of psychiatric illness, history of seizure or alcohol abuse. Then, they were provided with a questionnaire and asked to tick on the true options regarding their health state. About 50 subjects were dealt on a daily basis and completed in around 10 days. The reassessment was repeated every 4 months with a total of four assessments done by the same medical officer. Two assessments were done in Nepal at Shree Birendra Hospital (before commencing treatment and after completion of the regimen); rest two assessments were done in Sudan.

Any participant having three or more criteria positive in GHQ was identified as positive. The positive cases were followed up closely, keeping their identity a secret by supervising medical officer in Sudan. Among positive cases, mefloquine was stopped and provided with protective measures for a mosquito bite. The follow up (twice a week) and counseling about the side effects of mefloquine helped most of the positive cases, while in one of them tablet diazepam 5 mg was given for sleeplessness and anxiety for 5 days. All cases were followed up four-monthly and their physical and psychological conditions were closely observed. All patients were provided with medication under direct supervision. Being army personnel was the one who gets exposed to long term prophylactic mefloquine therapy and most previous study were a case based this study was carried out.

The institutional ethical review committee of NAIHS granted the ethical clearance to conduct this study. The Nepal army corps, Director General of Medical Services (DGMS) gave the permission to conduct the study. Explained written consent was taken from all the participants voluntarily.

## RESULTS

Out of the total 524 soldiers enrolled, 520 were male and rests 4 were females. There were 4 positive cases with a GHQ score  $\geq 3/12$ . Each positive case reported multiple adverse events. The incidence rate of mefloquine-associated neuropsychiatric manifestations is 7.6 cases per 1,000 study populations. Mean age was  $32.26 \pm 4.62$  years with age ranging from 23-53 years.

**Table 1: Mefloquine-associated adverse manifestations**

Adverse events	Number (s)	%
Neuropsychiatric adverse events		
Insomnia/sleep disturbances	3	0.57
Headache	3	0.57
Memory impairment, confusion	2	0.38
Dizziness or vertigo	2	0.38
Blurred or double vision	2	0.38
Difficulty in concentration	1	0.19
Abnormal dreams	1	0.19
Aggression	1	0.19
Psychotic episodes	1	0.19
Mood swings/changes	1	0.19
Loss of coordination	1	0.19
Suicidal ideation	1	0.19
Non-neuropsychiatric adverse events		
Disturbances in heartbeat	2	0.38
Fatigue, malaise	1	0.19
Neck pain	1	0.19
Abdominal pain, diarrhea	1	0.19
Muscle and joint pain	1	0.19

Among the different adverse events reported, neuropsychiatric adverse events were quite more frequent than non-neuropsychiatric adverse events. None of the reported adverse events were of life-threatening severity. Among different reported neuropsychiatric adverse events, insomnia/sleep disturbances and headache were more common (n=3) followed by memory impairment, confusion, dizziness or vertigo and blurred or double vision (n=2) while among non-neuropsychiatric adverse events, disturbance in heartbeat was common (and=2) (Table 1.).

## DISCUSSION

In the United Nations (UN) peace mission, Nepalese soldiers gets deployed in the countries allocated by the UN<sup>1</sup>. Mefloquine is one of the prophylactic medications recommended by the government of Nepal for soldiers going into different malarious countries in Africa<sup>8</sup>.

Mefloquine has a long elimination half-life of 14 to 41 days, which allows for once-a-week dosing and makes it a popular choice as malaria prophylaxis for travelers to malaria-endemic areas<sup>5</sup>. The current recommended prophylactic dose is 250 mg once a week for adults<sup>9</sup>. Since mefloquine was introduced in 1985, the most commonly reported adverse events were gastrointestinal and neuropsychiatric events<sup>7,10</sup>. Psychiatric symptoms after taking mefloquine range from restlessness, aggression, unease, a sense of impending doom, phobias, magical thinking<sup>12</sup>, agitation<sup>10,11</sup>, memory impairment<sup>11,12</sup>, auditory or true visual hallucinations<sup>15,16,20,21</sup> frequently involving religious or morbid themes<sup>11</sup>, insomnia<sup>10,16,21,22</sup>, abnormal dreams<sup>11,12,15</sup>, anxiety<sup>12,13,15</sup>, paranoia<sup>13,14</sup>, panic attacks<sup>14,15,19</sup>, personality change<sup>12,13,15</sup>, dizziness<sup>17,19,21,24,25</sup>, psychotic behaviour<sup>19,21-24,27</sup>, suicidal ideation<sup>19,22-24,27</sup> and suicide<sup>13,14,22,23</sup>, delusions<sup>17,19,23,25-27</sup>, persecutory mania<sup>16,19,24-27</sup>, depression<sup>22-27</sup> to hallucinations<sup>15,22,24-27</sup> and sleep disturbances<sup>19,21,24-26</sup>. Such symptoms have been reported after only a single 250-mg tablet and may progress in severity with subsequent doses. In some cases, these symptoms have been reported to continue for months or years after mefloquine has been stopped<sup>16</sup>.

Neurologic symptoms such as tinnitus<sup>10</sup>, dizziness<sup>10,12,24</sup> or vertigo<sup>10,14,22</sup>, convulsions<sup>14,19,21,24,25</sup> and loss of balance<sup>13, 15,19,20</sup> may develop. During prophylactic use, if above mentioned neurologic symptoms occur, the drug should be discontinued, and an alternative medication should be substituted.<sup>15</sup> In the present study, in all four cases, mefloquine was held and only preventive ways like the use of mosquito repellent and net were used. Mefloquine is highly effective in preventing malaria, but articles in the medical and lay press that highlight the neuropsychiatric side effects of mefloquine have caused many travelers to use less-effective alternatives or to avoid chemoprophylaxis altogether<sup>6</sup>. This large study on Nepalese troops deployed in UN peace mission found mefloquine to be relatively safe in an apparently healthy population with only four (7.6/1,000) positive cases with GHQ  $\geq 3$ . Among neuropsychiatric adverse events associated with mefloquine, insomnia/sleep disturbances and headache were more common (and=3) followed by memory impairment, confusion, dizziness or vertigo and blurred or double vision (n=2)

in the present study. Additionally, most of the previous adverse events related reports on mefloquine were case based studies<sup>18-21,23</sup>. So, with proper screening of the individual to rule out any systemic illnesses, mefloquine can be used safely as a prophylactic agent while moving to malarious prone zone judging the benefit over the risk.

This study was based on Nepalese troops posted in Sudan for UN peace mission taking mefloquine as prophylactic regimen so its major limitation could be its generalizability to all populations and ethnicity. So, randomized study including different population is the next step ahead to explore the safety of mefloquine.

## CONCLUSION

Mefloquine can be safely used in apparently healthy

individuals where malaria is endemic with a high prevalence rate, judging the benefit over the risk of not using it. Individuals should not avoid chemoprophylaxis with mefloquine based on unnecessarily sensationalized media coverage. Though this non-randomized study; based on Nepalese adult population (soldiers) its generalizability may not be applicable in all population groups so further well-designed study including other ethnic population is next to explore the safety of mefloquine.

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