MEFLOQUINE – NEUROPSYCHIATRIC SIDE EFFECTS PROFILE

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ABSTRACT

Background: Mefloquine is a drug widely used for prophylaxis and treatment of malaria. The current study was aimed at finding out the common neuropsychiatric side effects in Pakistani troops serving abroad on United Nations peace keeping mission in malaria endemic areas and to prescribe alternative therapy in individuals more susceptible to these side effects.

Patients and Methods: In a case control study 76 subjects taking mefloquine on weekly basis and reporting sick to the hospital were assessed for neuropsychiatric symptoms and compared with another 50 subjects not on this drug. This study was conducted at Pak-Field Hospital at Siera leone during 2003 to 2004.

Results: Sleep disturbances were found in 52.63%, while 60.52% had depressive and other mood related disorders. Anxiety was present in 35.52% whereas 6.57% subjects had psychotic symptoms. Other neurological symptoms like headache and tremors were common. General fatigue was seen in 61.84% of cases. Visual disturbances, delirium and seizure were not significant in our study.

Conclusion: Mefloquine therapy in malaria is frequently associated with serious toxic and neurological side effects. An alternative regimen for prophylaxis and treatment is recommended in subjects who have history of mood disorders, paranoia, anxiety and convulsions.

Keywords: Mefloquine, neuropsychiatric side effects, malaria prophylaxis

INTRODUCTION

Each year an estimated 50 million travellers visit malaria endemic areas. Around 30000 cases of malaria are reported annually in non endemic, industrialized countries and this imported malaria remains a public health problem with its high mortality [1]. Recommendations vary widely as to optimum prophylactic treatment for the travellers to high risk endemic areas such as Sub Saharan Africa which includes Sierra leone. Four regimens are currently available, Mefloquine, combined Atovaquone and Proguanil, Doxycycline and combined Chloroquine and Proguanil [2-5]. Mefloquine is used as the standard malaria prophylaxis in the troops of Pakistan military contingent deployed at Sierra leone. The drug, Mefloquine, a compound structurally related to quinine, is used for the prophylaxis and treatment of Plasmodium falciparum and Plasmodium vivax malaria [6]. The recommended adult prophylactic dose is 250 mg once a week, starting one week before entering an area where chloroquine resistant malaria is endemic and continuing until 4 weeks after departing it [7]. Mild, transient adverse effects such as nausea and dizziness occur in about 40% of the patients [8]. Serious neuropsychiatric adverse effects e.g. psychosis, encephalopathy and convulsions occur in about 4-7 patients in 1000 given mefloquine to treat malaria and about 1 in

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1300 patients taking it for prophylaxis [9]. Other possible adverse effects include, sleep – wake rhythm disturbances, anxiety, panic attacks, mood disturbances, acute psychosis, confusion/ delirium, headache, tremors, ataxia, fatigue, visual disturbances and seizures [10].

The aim of the study is to determine the common neuropsychiatric manifestations and the importance of the awareness of these side effects, so that individuals, who develop these manifestations or are susceptible to have these side effects, should preferably be put on the alternative malaria prophylactic therapy.

PATIENTS AND METHODS

This is a comparative study, conducted at Pak Field Hospital at Sierra leone from Oct 2003 to Apr 2004. All the subjects included in this study were the young male Pakistani soldiers of the age group 24 – 38 years .They were all considered physically fit as they were thoroughly examined for any medical or psychiatric illness before entering the mission area. A total of 76 patients (n=76) who reported sick to the hospital and in whom, after careful history and examination no organic basis of their symptoms could be found, were reassessed by the psychiatrist Pak Field Hospital. All these subjects were taking tab mefloquine 250mg weekly for the last 2 months or more. Although the serum levels of mefloquine could not be done in order to determine their compliance but since they were strictly taking the medicine under supervision so they were assumed as compliant. The patients were allowed sufficient time to give an elaborate account of their symptoms and these were noted on a separate performa. At the end, few direct questions were also asked to include /exclude any important negative or positive finding.

Similarly another 50 patients (c=50) were taken as control, who reported sick to the hospital but due to certain reasons were not taking tab mefloquine over the last 2 months or have been using tab doxycycline as an alternative for malaria prophylaxis. The following neuropsychiatry symptoms were assessed by the psychiatrist and their presence or absence was noted in both the groups.

- sleep disturbances
- anxiety
- depression/ mood related symptoms
- acute psychotic symptoms
- headache
- tremors
- numbness and tingling in extremities
- fatigue
- vertigo/ ataxia
- visual disturbances
- confusion/ delirium
- seizures/ fits

The above mentioned neuropsychiatric symptoms are those which are found in literature regarding mefloquine.

The data obtained was subjected to statistical analysis using SPSS (ver 10.0), P value was determined by using x-test and the results were drawn accordingly.

RESULTS

A total of 126 patients were subjected to the study and all of them were males. The mean age of the sample was 29.4 years. The number of patients(n=76) which were taking mefloquine, 250 mg weekly, for the past 2 months or more had variable overlap of symptoms. Majority of them had two or more neuropsychiatric symptoms at the time of interview. Sleep disturbances were found in 40 patients (52.63%) as compared to 8 patients (16%) in the control (the predicted p value is < 0.05). Similarly 27 patients (35.52%) had symptoms related to anxiety whereas only 3 patients (3.94%) had panic attacks. Depression and mood related symptoms were found in 46 patients (60.54%) as compared to 11 patients (22%) of the control (p-value <0.05).

Acute psychotic symptoms were seen in 5 patients (6.57%) whereas none in the control had psychotic symptoms. Headache and fatigue were found in 56.57% and 61.84% of the subjects respectively and both had p values <0.05. Tremors were found in 13 patients (17.10%) (p-value < 0.05). The symptoms of numbness and tingling in the extremities was present in 19 subjects (25%) (p value <0.05). However symptoms like visual disturbances, confusion and seizures were not statistically significant and their p value was >0.1. The data and its statistical significance is shown in table.

Table: Symptoms and statistical significance

Symptom	Mefloquine (n=76)	Control (c=50)	P value (paired T test)	Statistical significance
Sleep disturbance	40	8	< 0.05	VS
Anxiety	27	5	< 0.05	VS
Panic attacks	3	2	> 0.05	NS
Mood related symptoms	46	11	< 0.05	VS
Acute psychotic symptom	5	0	> 0.1	NS
Headache	43	13	< 0.05	VS
Tremors	13	1	> 0.05	NS
Numbness	19	2	< 0.05	VS
Fatigue	47	7	< 0.05	VS
Vertigo/ataxia	15	1	< 0.05	VS
Visual disturbances	1	2	> 0.05	NS
Confusion/ delirium	1	0	> 0.05	NS
Seizures/ fits	0	0	> 0.05	NS

DISCUSSION

In a large study by Barret [11] the side effects of mefloquine were found to be 40%, although majority of them were trivial, however 0.7% had serious disabling neuropsychiatric symptoms. This figure is less than the figures of our study, the probable reason for that is Barette in his study surveyed the travellers who visited the endemic areas and used mefloquine and the method of reporting was voluntary. In our study the troops were compulsorily given tab mefloquine and they reported sick to the easily approachable medical facility for any untoward symptom they experienced.

In another study by Corbett [12] the rate of reported side effects was high. Seventy one percent respondents who had taken mefloquine reported one or more side effects. Depression and anxiety were common in those who had taken mefloquine (20%). In our study the depression and other mood related symptoms were prominent (60.52%) whereas anxiety was found out to be 35.52%.

Women taking mefloquine are significantly more likely to have moderate neuropsychological problems [13]. However our study does not depict any gender based variations in the symptoms as no female patient was included in the study. In another randomised double blind clinical trial on 359 US marines taking mefloquine showed increased incidence of dizziness and in coordination [14], but not to the extent of functional compromise. Sleep disturbance and increased dream activity was also noticed. Similarly in our study vertigo and ataxia were present in 19.73% of the subjects and sleep disturbances were found in 52.63% of the troops.

In a review article [15] the spontaneously reported 59 serious neurological and psychiatric adverse effects of mefloquine reported over a time period of 5 years are: 26 convulsions, 12 severe depression, 20 psychotic episodes and 1 toxic encephalopathy. The precise mechanism of serious neurological and psychiatric reaction is unknown; however the high risk factors may be history of seizures or manic depressive illness. Hence mefloquine prophylaxis should not be prescribed to such patients. Although in our study no such serious side effects were noted but caution should be taken in using mefloquine in those subjects who already have shown mild reaction to this drug.

Interestingly in our study no patient expressed any suicidal idea or thought even on direct questioning. In various other studies

and media reports mefloquine has been implicated in suicidal risk [16].

CONCLUSION

Since the Pakistani troops are increasingly exposed to the malaria endemic areas such as Sub Saharan African countries due to their commitments in United Nations peace keeping missions, there is a dire need for malaria prophylaxis. Mefloquine has been generally recommended for malaria prophylaxis but it has increasingly been associated with toxic CNS side effects such as psychosis, aggression, mood disorders and neurological disorders. If psychiatric symptoms occur while taking mefloquine, the drug should be immediately stopped and malaria prophylaxis should be continued with alternative medicines.

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