

Epilepsy triggered by mefloquine in an adult traveler to Uganda

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Author contributions: Gobbi F wrote the manuscript; Rossanese A and Postiglione C managed the patient; Buonfrate D and Angheben A performed the literature search; Bisoffi Z revised the manuscript; all authors have read and approved the final version to be published.

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Received: September 25, 2013 Revised: November 7, 2013

Accepted: December 12, 2013

Published online: January 16, 2014

Abstract

We report a case of a traveler who visited Uganda for 8 d, and took mefloquine one tablet/week for malaria prophylaxis. After the second dose, he suffered from two episodes of loss of consciousness with seizures, therefore mefloquine was discontinued. During the flight back after full recovery, seizures reoccurred while he was on board, he was disembarked in Addis Ababa and then transferred to Nairobi. After repatriation to Italy, he experienced four other similar episodes. The patient was still on full dose anticonvulsant therapy one year and a half after, as any attempt at reduced dose was unsuccessful. Currently, three agents (mefloquine, atovaquone/proguanil, and doxycycline) are recommended for malaria chemoprophylaxis, with similar efficacy but different adverse event profiles, regimens, and prices. Considering that mefloquine is associated with a higher risk of neurologic and psychiatric adverse events than the alternative regimens, we suggest considering mefloquine as a second line choice after atovaquone/progua-

nil and doxycycline for short-term travelers.

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Key words: Mefloquine; Neuropsychiatric disorders; Epilepsy; Antimalarial chemoprophylaxis; Side effects

Core tip: We report a case of epilepsy due to mefloquine chemoprophylaxis. Considering that mefloquine is associated with a higher risk of neurologic and psychiatric adverse events than the alternative regimens, we suggest considering mefloquine as a second line choice after atovaquone/proguanil and doxycycline for short-term travelers.

Gobbi F, Rossanese A, Buonfrate D, Angheben A, Postiglione C, Bisoffi Z. Epilepsy triggered by mefloquine in an adult traveler to Uganda. *World J Clin Cases* 2014; 2(1): 12-15 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v2/i1/12.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v2.i1.12>

INTRODUCTION

According to most international guidelines^[1-4], atovaquone/proguanil, doxycycline and mefloquine are all indicated as the first choice for the chemoprophylaxis of *Plasmodium falciparum* malaria. The efficacy of the three drugs seems to be comparable^[5], but side effects and costs are different. Although a causal relationship between the drug intake and a severe side effect is usually difficult to demonstrate, it is well known that mefloquine is associated with a high risk of neurologic and psychiatric disorders (NPD). Weinke *et al*^[6] estimated that one of 13000 travelers receiving mefloquine chemoprophylaxis suffers from serious central nervous system reactions. Barrett *et al*^[7], in a postal and telephone survey, reported that 0.7% of

travelers taking mefloquine had disabling NPD.

Adverse events related to mefloquine mostly occur in people with a past history of seizures or manic-depressive illness^[8], but in literature there are reports of cases of seizures in travelers, with no previous personal or family history of epilepsy, after taking mefloquine for treatment^[9] or prophylaxis^[10].

CASE REPORT

A 40-year-old Italian traveler visited Uganda for 8 d, and took mefloquine one tablet/week for malaria prophylaxis. His weight was 70 kg. His clinical history was unremarkable and he had no history of alcohol or tobacco abuse. He was vaccinated against yellow fever, hepatitis A and tetanus-diphtheria. Upon arrival in Kampala, after the second dose of mefloquine, he suffered from two subsequent episodes of grand mal seizure, therefore mefloquine was discontinued. The duration of the two episodes was about 5 min and the patient remained unconscious for 10 min. During the flight back after full recovery, seizures reoccurred while he was on board, so he was disembarked in Addis Ababa. One further episode occurred at the airport and another one upon urgent admission to the hospital. He was then transferred to Kenya Nairobi Hospital under suspicion of meningitis or cerebral malaria (both were later ruled out), where he started on phenytoin 100 mg twice a day.

After repatriation to Italy, two weeks after the first crisis, an electroencephalogram showed diffuse epileptiform abnormalities, while a brain-RM was negative. Then, he experienced four similar episodes and was treated with diazepam. Moreover, phenytoin was replaced by levetiracetam 500 mg twice a day. Levetiracetam was stopped after 6 mo, but subsequent seizure episodes required another course of anticonvulsant prophylaxis, with sodium valproate 500 mg twice a day. The patient was still on full dose anticonvulsant therapy one year later, as any attempt at dose reduction was unsuccessful.

DISCUSSION

Currently, three drugs (mefloquine, atovaquone/proguanil, and doxycycline) are recommended for malaria chemoprophylaxis, with similar efficacy but different adverse event profiles, regimens, and prices^[5]. The choice of the different drugs depends on the levels of malaria transmission and presence of drug resistance in the destination area, on specific characteristics of the traveler (*e.g.*, underlying health conditions, possible pregnancy, compliance to daily/weekly therapies), on the duration and purpose of travel and on costs. Jacquerioz *et al.*^[11], in a review of drugs for preventing malaria in travelers, conclude that atovaquone-proguanil and doxycycline are the best tolerated agents and mefloquine is associated with

adverse NPD. NPD includes two categories of symptoms: central and peripheral nervous system disorders (including headache, dizziness, vertigo, seizures) and psychiatric disorders (including major psychiatric disorders, anxiety and sleep disturbances)^[12]. Controlled studies have shown a significant excess of NPD in mefloquine users^[5,13-16]. Moreover, in a recent study, van Essen *et al.*^[17] suggest that mefloquine disturbs motor learning skills. Considering NPD as potentially severe and dangerous adverse side effects and the availability of drugs with equivalent efficacy, the new Italian indications for malaria prophylaxis^[18] proposed mefloquine as a second line choice after atovaquone/proguanil and doxycycline for short-term travelers. However, mefloquine keeps playing a fundamental role for specific groups of travelers: pregnant and breastfeeding women, long-term travelers, adults and children visiting friends and relatives (VFR)^[19]. Travelling to malaria endemic areas during pregnancy is contraindicated because this disease is an important cause of stillbirth, spontaneous abortion or maternal death^[20]. However, for pregnant women who cannot defer their travel (mostly VFR), mefloquine is the only option, as doxycycline is contraindicated in pregnancy and, although proguanil is considered safe and no teratogenicity has been observed in animal studies using atovaquone, there are no sufficient data about safety of atovaquone/proguanil. In fact, mefloquine has been proved to be safe in the first trimester: according to Schlagenhauf *et al.*^[21], birth defect prevalence and fetal loss after mefloquine exposure in pregnancy were comparable in prospectively monitored cases to background rates. For long-term travelers (nonimmunized travelers who visit malaria endemic areas for a period of six mo or longer), malaria chemoprophylaxis is controversial. Although the risk of malaria increases with longer stays, the adherence to chemoprophylaxis decreases over time. Steffen *et al.*^[22] reported that compliance with chemoprophylaxis was reported by 57.0% of travellers who spent less than 3 mo in Africa, compared with 29.2% who stayed for 3-12 mo. In case chemoprophylaxis is recommended, mefloquine, if well tolerated, remains a good option in alternative to doxycycline: the weekly dose facilitates a good adherence. Long-term atovaquone/proguanil is now registered in Italy, but a long-term chemoprophylaxis is too expensive. van Riemsdijk *et al.*^[16] found that NPD occurred more frequently in females and were more common in first-time users. Usually females weigh less than males, so we suggest to modulate the mefloquine dosage by body weight (*i.e.*, people weighing between 40 and 60 kg should take 75% of the tablet^[4]). For a traveler who takes mefloquine for the first time, it is advisable to start chemoprophylaxis 3 wk before travelling, because adverse effects usually appear at the first dose. Lobel *et al.*^[23] found that the frequency of these events declined with the increasing duration of prophylaxis. Travelers who have taken mefloquine before and had no NPD can usually take this drug again. For many VFR families,

who stay long in high-risk areas, mefloquine represents a good option because of its low cost and weekly administration. Moreover, mefloquine is effective and well tolerated in children weighing < 20 kg^[24]. Considering that mefloquine is often the only drug that can be prescribed for young children VFR, because doxycycline is contraindicated in children < 8 years and atovaquone/proguanil is generally too expensive, mefloquine is considered the best option for VFR families.

In conclusion, we suggest considering mefloquine as a second choice for short-term (less than one mo) travelers; however, mefloquine remains a good option, in alternative to doxycycline, for long-term travelers and the first choice for pregnant women and VFR families.

COMMENTS

Case characteristics

Grand mal seizures after taking mefloquine for malaria prophylaxis.

Clinical diagnosis

The duration of each of the two episodes of grand mal seizures was about 5 min and the patient remained unconscious for 10 min.

Differential diagnosis

Epilepsy due to other causes.

Imaging diagnosis

Electroencephalogram showed diffuse epileptiform abnormalities, while a brain-RM was negative.

Treatment

The patient was treated with phenytoin 100 mg twice a day, then with levetiracetam 500 mg twice a day, and then with sodium valproate 500 mg twice a day.

Related reports

Adverse events related to mefloquine mostly occur in people with a past history of seizures or manic-depressive illness, but in literature there are also reports of cases of seizures in travelers who had no previous personal or family history of epilepsy, after taking mefloquine for treatment or prophylaxis.

Experiences and lessons

Authors suggest considering mefloquine as a second choice for short-term (less than one mo) travelers; however, mefloquine remains a good option, in alternative to doxycycline, for long-term travelers and the first choice for pregnant women and visiting friends and relatives families.

Peer review

This article highlights possible severe side effects of mefloquine and suggest to consider other drugs as a first choice for malaria chemoprophylaxis.

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