

CASE REPORT

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Failure of malaria chemoprophylaxis with mefloquine in an oversize traveller to Mozambique

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Abstract

A case of failure of mefloquine prophylaxis in an oversize traveller, who correctly took the drug. This case seems to be attributed to mefloquine resistance, however it is suggested that mefloquine dosage should be modulated by body weight, as is already indicated by some authorities.

Keywords: Failure, Mefloquine, Chemoprophylaxis, Malaria

Background

The correct dosage for mefloquine in anti-malarial chemoprophylaxis is 5 mg/kg [1]. The vast majority of international [2,3] and national [4] guidelines on malaria prevention suggests a prophylactic dose of 250 mg per week in adult travellers. However, regardless the product label, some national Travel Medicine Societies, such as the Swiss and the Austrian ones, suggest to modulate the drug dosage by body weight (Table 1) [5,6]: 1 ½ tablet per week for patients weighing > 90 kg, two tablets per week for the patients weighing > 120 kg. The dosage issue concerns not only the overweight, but also the low weight travellers. Those weighing < 60 kg may poorly tolerate a whole tablet of mefloquine per week [7-9].

A case is presented of mefloquine failure in an oversize traveller, that was initially attributed to insufficient dosage.

Case presentation

A 50-year-old Italian patient was admitted to the Centre for Tropical Diseases (CTD) with fever (39°C) and diarrhoea since three days. He reported having visited many Catholic missions over several years (he is a priest) in sub-Saharan Africa, Asia and Latin America. The average length of stay was between 10 and 14 days. He had been vaccinated against yellow fever, hepatitis A and B, and typhoid fever. From 20th to 31st March 2012, he had travelled to Mozambique, regularly taking malaria chemoprophylaxis with mefloquine, one tablet (250 mg) weekly, starting

one week before travelling and continuing for four weeks after return: he took the last tablet on 24th April. He presented to CTD on May 18th 2012. His weight was 144 kg. He had no history of alcohol, tobacco or illicit drugs abuse. He was not under any long-term medication. The heart rate was 90 beats per minute and the blood pressure 140/70 mm Hg. Physical examination was unremarkable, except for a distended abdomen. Quantitative buffy coat (QBC), antigen malarial test and blood smears resulted positive for *Plasmodium falciparum* malaria, with a parasitaemia of 0.13% (6330 /μl). The blood tests showed 7430 WBC/μl, C reactive protein 142 mg/L. The patient was treated with artemether (tablet 50 mg), eight tablets the first day, then three tablets/day until the fifth day, followed by four tablets of sulphamethoxypyrazine/pyrimethamine 500 mg/25 mg (artemisinin-based combination artemisinin-based combination therapies were not yet available). After two days of treatment, blood films resulted negative and remained so at follow-up, one month later.

Whole blood and plasma mefloquine concentrations were retrospectively evaluated on cryo- preserved (-80°C) samples taken on admission (25 days after the last mefloquine intake), by high pressure liquid chromatography (HPLC) coupled with ultraviolet diode-array detection [10,11].

Whole blood and plasma mefloquine concentrations were 516 and 320 ng/mL, respectively.

Discussion

Despite a correct anti-malarial chemoprophylaxis, the patient developed *P. falciparum* malaria. Therefore, it was concluded that either the strain of *P. falciparum* was

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Table 1 Dosage of mefloquine tablet (250 mg) in Swiss/Austrian malaria prophylaxis recommendations

> 120 kg	2 tablets (twice weekly on tablet: e.g. Mon & Thu)
> 90 kg	1 and ½ tablets (twice weekly on tablet: e.g. Mon & Thu)
> 60 kg	1 tablet
40-60 kg	¾ tablet
20-40 kg	½ tablet
10-20 kg	¼ tablet
< 10 kg	5 mg /kg

resistant to mefloquine, or its dose was insufficient according to the patient's body weight. At first, the failure was attributed to an insufficient dosage according to the patient's weight (144 kg), but later mefloquine concentration was assessed on pre-treatment plasma and blood samples that had been stored.

The mefloquine level in the patient's bloodstream at admission was within the expected range, considering the breakthrough mefloquine levels >620 ng/ml and a half-life of 21 days (Product information Lariam®, Roche, the Netherlands). Considering these data, *P. falciparum* resistance to mefloquine was more probable, despite the limitation of a single point in time determination.

A review of literature was performed to collect the characteristics and probable causes of reported cases of failure of mefloquine prophylaxis. PubMed was searched using the following keywords: mefloquine, chemoprophylaxis, failure, Africa. Thirteen papers were retrieved [12-24], describing a total of 31 cases (Table 2).

Only three cases were reported in the last 15 years, while the others were reported between 1990 and 1998. In most of the cases (25/31) the infection had been acquired in West Africa, in six cases in East Africa (one each in Malawi, Tanzania, Madagascar, Mozambique, and two in Somalia). Six patients were females and 25 males; six were children and 25 were adults between 18 and 50 years of age. Three patients developed *P. falciparum* malaria while in the endemic country, 28 patients after return. In the latter group, 16 travellers became ill within four weeks after return (still under prophylaxis) and 12 developed the disease after the last dose of mefloquine. The median onset of symptoms after return was 28 days (range 3–91 days). In all cases resistance to mefloquine was presumed, although for some of them drug concentration in plasma was not available.

In relation to the first suspicion, there is no agreement on the need to adjust mefloquine regimen to body weight. It is worth considering this factor, though, also taking into account the lipophilic behaviour of this drug, which has an apparent volume of distribution between 13 to 40 l kg⁻¹ with a mean of 20 l kg⁻¹. Both apparent volume of distribution and individual systemic clearance are probably influenced by body fat, thus causing different pharmacokinetic profiles [7,25,26].

In conclusion, although in this case the failure of mefloquine prophylaxis was most probably due to drug resistance, the indication given by some scientific societies that mefloquine dosage should be modulated by body weight seems reasonable and should probably be considered in new guidelines.

Table 2 Papers describing mefloquine prophylaxis failure in travellers to Africa

Author	Age	Sex	Country of infection	Symptoms onset (before return)	Symptoms onset (days after return)
Callen (2006)	25	M	Gambia	-	4
Wichmann (2003)	44	F	Tanzania	-	23
Gary-Toussaint (2002)	45	M	Senegal	-	41
Gizolme (1998)	40, 12, 9	F, M, F	Togo	-	63, 77, 91
Lobel (1998)	31, 22, 30, 26, 25	M, M, M, F, M	Niger, Sierra Leone, Cameroon, RCA	Y	-
Matteelli (1995)	20	M	Mozambique	-	3
Magill (1993)	23	M	Somalia	Y	-
	21	M	Somalia	Y	-
Raccurt (1991)	3, 30, 28, 22, 40, 44, 23, 23, 27	F, M, M, M, M, M, M, M, M	Senegal, Burkina Faso, Niger, Nigeria, Mali, Ivory Coast, Togo	-	3, 4, 6, 13, 15, 19, 21, 25, 26
Ringwald (1990)	5, 28, 34, 37	M, M, M, M, M	Burkina Faso, RCA, Madagascar, Togo	-	19, 26, 31, 32
Ooi (1991)	26	M	Malawi, Kenya	-	21
Durieux (1990)	18	M	Burkina Faso	-	58
Gay (1990)	6	M	Senegal, Ivory coast	-	55
Bricaire (1990)	6, 34, 40, 45, 50	M, M, M, M, F	Mali, Sierra Leone, Senegal, RCA	-	7, 30, 45, 46, 61

Consent

Written informed consent was obtained from the patient for the publication of this report.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

FG, AR visited and followed-up the patient. AA and DB performed Pubmed search. FG and DB have been involved in drafting the manuscript. GL detected drug concentration. ZB and AA revised the manuscript critically for important intellectual content. All the authors have given final approval of the version to be published.

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