Dermatological adverse effects with the antimalarial drug mefloquine: a review of 74 published case reports

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Summary

Mefloquine is a relatively new antimalarial drug which has been associated with a wide variety of adverse effects, including skin reactions. In order to evaluate the range and frequency of mefloquine's dermatological effects, we searched the scientific literature for published case reports of such effects. We found 74 case reports, published between the years 1983 and 1997. Pruritus and maculopapular rash are the dermatological effects most commonly associated with mefloquine: their approximate frequency is 4-10% for pruritus, and up to 30% for nonspecific maculopapular rash. Adverse effects associated less commonly with mefloquine include urticaria, facial lesions and cutaneous vasculitis. One case of Stevens–Johnson syndrome and one fatal case of toxic epidermal necrolysis occurred. Appropriate primary studies of mefloquine use should be carried out to elucidate the epidemiology and aetiology of dermatological and other adverse effects of the drug.

Introduction

Mefloquine (Lariam–Roche) is a potent antimalarial drug of the arylamino alcohol class that is chemically related to quinine. It is only available as an oral preparation. Mefloquine is highly lipid-soluble, and is metabolized largely in the liver; it has an elimination half life of 2–3 weeks.[1] Its mechanism of action against malaria parasites is unknown.[2]

Mefloquine has been used to treat *Plasmodium falciparum* malaria since 1980, and has been prescribed prophylactically in travellers since 1986. In the treatment of malaria, mefloquine is usually administered in adults as a five-tablet once-only dose, which is sometimes divided into two parts in an attempt to minimize side-effects.[3] In malaria prophylaxis the drug is normally prescribed at an adult dose of one 250 mg tablet per week, on account of its long half-life.[4] To date, approximately 12 million travellers worldwide have received mefloquine prophylaxis.[5]

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Recently there has been concern in the lay press and media regarding the side-effects of mefloquine.[6] Attention has focused on the neuropsychiatric effects of the drug, which are principally insomnia and fatigue.[7] However, there have been lay reports of dermatological reactions as well, such as 'skin rashes'[8] and 'itching skin'.[9] Such reactions to mefloquine have not as yet been described in the standard textbooks of dermatology.

Within the UK the Medicines Control Agency runs a 'yellow card' voluntary reporting system for identifying adverse drug reactions. Although the rate of reporting in such a system is inherently low it has drawn attention to important associations such as oral contraceptives and thromboembolism. Up to July 1998 a total of 1549 reports relating to mefloquine were received including eight fatal reactions (personal communication). These listed a total of 4402 reactions relating to all organ systems: of these 233 were specific for the skin and subcutaneous tissues. This data is of course not peer-reviewed.

We undertook a review of published peer-reviewed reports of dermatological adverse effects with mefloquine to assist clinicians who have to consider a drug eruption due to mefloquine in the differential diagnosis of a patient's rash.

Materials and methods

We searched Medline and Embase using the search terms 'mefloquine', 'adverse drug reactions', 'adverse effects', 'side-effects' and 'toxicity'. We did not apply any language restriction. Our final search was carried out on 15 September 1998.

Our electronic searching yielded 143 'hits', all of which we retrieved as full papers. Approximately one-half of these papers were reports of randomized controlled trials or observational studies in which the symptoms experienced by participants were documented as one of the study outcomes. Only a small number of these symptoms were dermatological.

We consulted the standard textbooks of dermatology and pharmacology, and scanned the citations of all the papers we had retrieved, in order to check for additional published reports on the dermatological adverse effects of mefloquine.

Results

We found a total of 74 published case reports of dermatological adverse effects of mefloquine. These reports were contained in 20 separate scientific papers, the first of which was published in 1983, and the most recent in 1997.[10–29] Two of the papers were in French and the remainder were in English. We did not find any case reports published in 1998.

Approximately one-half of the case reports of dermatological adverse effects were from papers describing randomized controlled trials of mefloquine. These studies, together with the main clinical details of all the case reports, are shown in Table 1.

Demographic characteristics of patients

The mean age of the patients, where this parameter was recorded, was 35.4 years; there were two children in the series. Most of the patients (72%) were male. The patients were divided into military personnel (61%), residents of malaria-endemic areas (24%), tourists (10%) and experimental volunteers (5%).

Total dose of mefloquine taken

The dose of mefloquine taken before the onset of dermatological symptoms was recorded in 21 cases: the mean was 585 mg, range 150–1250 mg. Of these patients, 42% had taken mefloquine prophylactically, and 58% as a treatment.

Onset of dermatological adverse effects

This parameter was recorded in 11 cases. The mean interval to the onset of dermatological symptoms after starting the drug was 11.5 days, range 2–35 days.

Dermatological features

The most common dermatological manifestation was pruritus, which was recorded in 31 (42%) of the reports. In six cases the pruritus was described as being 'intense', 'severe' or 'burning'.

Apart from pruritus, the most common dermatological effect of mefloquine use appears to have been a nonspecific maculopapular rash. There were two reports of cutaneous vasculitis,[22,25] and one report each of Stevens–Johnson syndrome and toxic epidermal necrolysis.[18,28] We found no published reports of alopecia secondary to mefloquine use.

Outcome

Two travellers were hospitalized as a result of their symptoms one with a fatal outcome as follows.

Case one
A 66-year old female Belgian tourist was taking mefloquine prophylactically. After her first mefloquine tablet she experienced a sore and blistering lower lip, which progressed to erythematous, ulcerating lesions of oral and nasal mucosa, arms, legs and back. She was diagnosed as having Stevens–Johnson syndrome and was treated with antihistamine and oral steroids; the symptoms resolved after 35 days.[18]

Case two
A 6-year old female tourist was taking mefloquine prophylatically. Thirty-five days after starting mefloquine she developed a rash that evolved, within 48 h, to toxic epidermal necrolysis. The patient died after 19 days despite admission to a paediatric intensive care unit.[28]

The other 73 patients appear to have recovered fully from their skin disorders, in most cases after discontinuation of mefloquine. A minority received active treatment as outpatients including oral and topical corticosteroids and oral antihistamines.

Discussion

This is the largest survey in the world literature of dermatological adverse effects attributed to mefloquine. While there is no obvious common pattern to the effects,

Table 1 Published case reports of dermatological adverse effects from mefloquine, 1983–97

Report	Patient type	Sex	Age (years)	Total dose of mefloquine taken	Mefloquine taken as prophylaxis or therapy	Onset of adverse effects (day)	Clinical summary
Ekue 1983*	Resident	M	?	1000 mg	Therapy	?	Itching and rash
Harinasuta 1983*	Resident	M	?	750 mg	Therapy	?	Itching, maculopapular rash, urticaria
Harinasuta 1985*	Resident	?	?	750 mg	Therapy	?	Rash (two reports)
De Souza 1987*	Residents	M	?	250/500/750 mg	Therapy	?	Pruritus (three reports)
Navaratnam 1989*	Military	M	?	?	Prophylaxis	?	Persistent severe skin rash with patches of erythema, intense pruritus (three reports)
Ajana 1990	Tourist	F	5	150 mg	Therapy	15	Status epilepticus, accompanied by transitory morbiliform rash
Shlim 1991	Tourist	F	23	500 mg	Prophylaxis	3	Burning sensation in face. Subsequently five red, raised, bullous lesions on face
Suriyamongkol 1991	Military	M	?	?	Prophylaxis	?	Rash (eight reports)
Van den Enden 1991	Tourist	F	66	250 mg	Prophylaxis	3	Erythematous/ulcerating lesions of lips, mucosa, arms. Stevens–Johnson syndrome
Doumbo 1992	Residents	?	?	?	Therapy	?	Moderate or severe pruritus (three reports)
	Residents	?	?	?	Therapy	?	Mild pruritus (six reports)
Looareesuwan 1992*	Resident	?	?	1250 mg	Therapy	2	Itching, with fine macular rash on extremities. self-limiting
Martin 1993	Tourist	M	42	750 mg	Prophylaxis	8	Erythematous, generalized, pruritic papular eruption. dry/cracked skin
Scerri 1993	Tourist	M	44	750 mg	Prophylaxis	15	Petechial eruption on upper lip. Itchy purpuric rash on legs. Cutaneous vasculitis
Luxemburger 1994*	Resident	?	?	?	Therapy	7	Urticarial rash
Croft 1995*	Military	M	?	?	Prophylaxis	?	Pruritus (10 reports)
White 1995	Tourist	F	62	1250 mg	Prophylaxis	22	Oedema and petechiae both legs. Cutaneous vasculitis
Buma 1996	Military	M	?	500 mg	Prophylaxis	8	Skin rashes (two reports)
Kollaritsch 1997*	Volunteers	?	?	250 mg	Prophylaxis	?	Cutaneous adverse reaction (four reports)
McBride 1997	Tourist	F	6	625 mg	Prophylaxis	35	Toxic epidermal necrolysis. Cardiac asystole, death.
Ohrt 1997*	Military	M	?	?	Prophylaxis	?	Skin-related adverse events (22 reports)

*Randomised control trial.

they appear to be mostly mild or moderate in intensity, and to be usually self-limiting. Dermatological symptoms can occur both when mefloquine is taken for the treatment of malaria, and at prophylactic dosages.

Pruritus is the most common dermatological symptom to be associated with mefloquine. One of the reports we identified was of a series of Africans treated with single-dose mefloquine for clinically confirmed malaria, and in this cohort the incidence of pruritus was 15%.[19] In a cohort of British soldiers taking mefloquine prophylactically for 12 weeks it was 7%.[24] These data are consistent with what is known of the side-effects of other antimalarial drugs, such as chloroquine, which are structurally related to mefloquine.[30]

The frequency of nonspecific maculopapular rash in mefloquine users is difficult to estimate from this survey. It may be as high as 10% at treatment doses,[12] and between 4 and 7% when mefloquine is taken prophylactically for short periods.[17,27] With prolonged prophylactic usage, rashes may be experienced by up to 30% of mefloquine users.[29]

We found no published reports of alopecia secondary to mefloquine ingestion, even though there have been spontaneous notifications to the manufacturer of alopecia in mefloquine users.[31] This suggests that alopecia either is not truly associated with mefloquine, or that it is an extremely rare side-effect of the drug.

In addition to pruritus and maculopapular rash, urticaria and facial lesions appear to be associated with mefloquine, although the numbers reported are small.[11,16,23]

There are two reports in the literature of mefloquine causing a cutaneous vasculitis.[22,25] One of these diagnoses was confirmed by skin biopsy.[25]

More worrying is the suggestion from this survey that mefloquine may very rarely give rise to serious skin eruptions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis. Such rare events have been reported with other antimalarial drugs, and were responsible for the withdrawal of sulfadoxine-pyrimethamine (Fansidar) as a prophylactic antimalarial drug for travellers.[32] With mefloquine each of these diagnoses has to date been reported once.[18,28]

When evaluating the harmful side-effects of a drug, questions of causality arise. Several of the papers we identified through this survey discuss causality in some depth. Martin *et al.*. point out that because of mefloquine's long half-life, there is the possibility that significant drug-induced toxic effects will occur many days after therapy has been discontinued.[21] This potentially long latent period may mask the close temporal association between drug ingestion and resulting effect which is normally one of the hallmarks of causality.

True adverse drug reactions (ADRs) should be verified through rigorous scientific methods such as experimental pharmacology, or epidemiologically through case–control studies nested within a large cohort study.[33,34] Alternatively, but yielding less strong evidence for causality, dechallenge–rechallenge tests should be undertaken in users of the drug under scrutiny.[35] These tests, however, are difficult to justify ethically in drugs such as mefloquine, which are commonly given to users who normally are well.[18]

The 74 case reports reviewed in this paper thus represent anecdotal evidence only that mefloquine can give rise to dermatological adverse effects, since the rigorous tests used to verify suspected ADRs have not yet been applied to mefloquine. We believe, however, that the relatively large size of this series, together with the fact that all of the reports we identified had been evaluated prior to publication through the critical peer review system, constitutes good circumstantial evidence that a truly causal relationship exists between mefloquine use and skin reactions in some susceptible individuals.[36] This association, and the pathophysiological mechanisms which underlie it, need to be elucidated through appropriate primary studies.[37]

Conclusion

There is good circumstantial evidence that mefloquine can cause mild and occasionally severe adverse dermatological effects in both healthy travellers and in hospital patients with malaria. These effects are mostly self-limiting and rarely require treatment. Pruritus is the most frequent dermatological reaction to mefloquine, and maculopapular rash is also common. Urticaria, facial lesions, cutaneous vasculitis, Stevens–Johnson syndrome and toxic epidermal necrolysis have all been associated with mefloquine. The incidence of dermatological adverse effects with mefloquine may be between 4 and 10% for short-term use of the drug, or as high as 30% for prolonged use. Primary studies of causality are needed in mefloquine users to verify the frequency and epidemiology of dermatological and other adverse effects of the drug.

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References

1 Desjardins RE, Pamplin CL, von Bredow J *et al*. Kinetics of a new antimalarial, mefloquine. *Clin Pharmacol Ther* 1979; **26:** 372–9.

2 Webster LT. Drugs used in the chemotherapy of protozoal infections. In: Goodman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics* 8th edn. New York: McGraw-Hill, 1992.

3 Murphy GS, Oldfield EC. Falciparum malaria. *Infect Dis Clin North Am* 1996; **10:** 747–55.

4 Bradley DJ, Warhurst DC. Guidelines for the prevention of malaria in travellers from the United Kingdom. *Commun Dis Rep Rev* 1997; **7:** R137–52.

5 Lobel Ho Kozarsky PE. Update on prevention of malaria for travelers. *J Am Med Assoc* 1997 **278** 1767–71.

6 Choo V. Uncertainty about mefloquine will take time to resolve. *Lancet* 1996; **347:** 891.

7 Croft A, Garner P. Mefloquine to prevent malaria: a systematic review of trials. *Br Med J* 1997; **315:** 1412–6.

8 Parris M. I think I'd rather have malaria. *Times Weekend Section (London)* 1998 April; **4:** 1–2.

9 Eaton L. Fly in the ointment. *Sunday Times Magazine (London)* 1998 May; **10:** 24–35.

10 Ekue JMK, Ulrich AM, Rwabwogo-Atenyi J, Sheth UK. A double-blind comparative clinical trial of mefloquine and chloroquine in symptomatic falciparum malaria. *Bull WHO* 1983; **61:** 713–8.

11 Harinasuta T, Bunnag D, Wernsdorfer WH. A phase II clinical trial of mefloquine in patients with chloroquine-resistant falciparum malaria in Thailand. *Bull WHO* 1983; **61:** 299–305.

12 Harinasuta T, Bunnag D, Lasserre R *et al*. Trials of mefloquine in vivax and of mefloquine plus 'Fansidar' in falciparum malaria. *Lancet* 1985; **i:** 885–8.

13 De Souza JM, Sheth UK, Wernsdorfer WH *et al*. A phase II/III double-blind, dose-finding clinical trial of a combination of mefloquine, sulfadoxine, and pyrimethamine (Fansimef) in falciparum malaria. *Bull WHO* 1987; **65:** 357–61.

14 Navaratnam V, Mohamad M, Hussain S *et al*. Chemosuppression of malaria by the triple combination mefloquine/sulfadoxine/pyrimethamine: a field trial in an endemic area in Malaysia. *Trans Roy Soc Trop Med Hyg* 1989; **83:** 755–9.

15 Ajana F, Fortier B, Martinot A *et al*. Prophylaxie par méfloquine et neurotoxicité. À propos d'une observation. *Semaine Des Hôpitaux Paris* 1990; **66:** 918–9.

16 Shlim DR. Severe facial rash associated with mefloquine. *J Am Med Assoc* 1991; **266:** 2560.

17 Suriyamogkol V, Timsaad S, Shanks GD. Mefloquine chemoprophylaxis of soldiers on the Thai-Cambodian border. *Southeast Asian J Trop Med Public Health* 1991; **22:** 515–8.

18 Van den Enden E, van Gompel A, Colebunders R, van Den Ende J. Mefloquine-induced Stevens–Johnson syndrome. *Lancet* 1991; **337:** 683.

19 Doumbo O, Doucoure O, Koita O *et al*. Efficacité et tolerance de la triple association méfloquine + pyrimethamine + sulfadoxine (Fansimef®) dans la traitement des accès palustres graves à Plasmodium falciparum au Mali (à propos de 100 cas). *Médecine D'afrique Noire* 1992; **39:** 458–62.

20 Looareesuwan S, Viravan C, Vanijanonta S *et al*. Randomised trial of artesunate and mefloquine alone and in sequence for acute uncomplicated falciparum malaria. *Lancet* 1992; **339:** 821–4.

21 Martin GJ, Malone JL, Ross EV. Exfoliative dermatitis during malarial prophylaxis with mefloquine. *Clin Infect Dis* 1993; **16:** 341–2.

22 Scerri L, Pace JL. Mefloquine-associated cutaneous vasculitis. *Int J Dermatol* 1993; **32:** 517–8.

23 Luxemburger C, ter Kuile FO, Nosten F *et al*. Single day mefloquine-artesunate combination in the treatment of multi-drug resistant falciparum malaria. *Trans Roy Soc Trop Med Hyg* 1994; **88:** 213–7.

24 Croft A. Toxicity of mefloquine is similar to that of other chemoprophylaxis. *Br Med J* 1995; **311:** 191.

25 White AC, Gard DA, Sessoms SL. Cutaneous vasculitis associated with mefloquine. *Ann Intern Med* 1995; **123:** 894.

26 Buma APCC, van Thiel PPAM, Lobel HO *et al*. Long-term malaria chemoprophylaxis with mefloquine in Dutch marines in Cambodia. *J Infect Dis* 1996; **173:** 1506–9.

27 Kollaritsch H, Que JU, Kunz C *et al*. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. *J Infect Dis* 1997; **175:** 871–5.

28 McBride SR, Lawrence CM, Pape SA, Reid CA. Fatal toxic epidermal necrolysis associated with mefloquine antimalarial prophylaxis. *Lancet* 1997; **349:** 101.

29 Ohrt C, Richie TL, Widjaja H *et al*. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997; **126:** 963–72.

30 Sowunmi A, Walker O, Salako LA. Pruritus and antimalarial drugs in Africans. *Lancet* 1989; **ii:** 213.

31 Palmer KJ, Holliday SM, Brogden RN. Mefloquine. A review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 430–75.

32 Miller KD, Lobel HO, Satriale RF *et al*. Severe cutaneous reactions among American travelers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986; **35:** 451–8.

33 Venning GR. Identification of adverse reactions to new drugs. IV — Verification of suspected adverse reactions. *Br Med J* 1983; **286:** 544–7.

34 Ashby D, Smyth RL, Brown PJ. Statistical issues in

pharmacoepidemiological case–control studies. *Statist Med* 1998; **17:** 1839–50.
35 Bégaud B, Evreux JC, Jouglard J, Lagier G. Imputabilité des effets inattendus ou toxiques des médicaments. actualisation de la méthode utilisée en France. *Thérapie* 1985; **40:** 111–8.
36 Haramburu F, Bégaud B, Péré JC. Comparison of 500 spontaneous and 500 published reports of adverse drug reactions. *Eur J Clin Pharmacol* 1990; **39:** 287–8.
37 Croft AM, Garner P, Squire SB. Malaria prevention for travelers. *J Am Med Assoc* 1998; **279:** 990.