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Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers

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See pp 528-530, 533

Abstract

Objective—To compare the frequency of adverse events, particularly neuropsychiatric effects, from mefloquine and from chloroquine plus proguanil as used for malaria chemoprophylaxis.

Design—Retrospective questionnaire to travellers taking either regimen between November 1993 and February 1995; telephone interview with those reporting pronounced side effects.

Setting—Travellers from Britain who consulted an advisory helpline.

Subjects—1214 adults taking mefloquine and 1181 taking chloroquine plus proguanil.

Main outcome measures—Reported presence of and degree of disability from 12 neuropsychiatric and other symptoms, as assessed by the subjects and by referees and on the basis of behaviour change.

Results—There were equal rates of any side effects (40%) and of stopping or changing medication. Overall, neuropsychiatric adverse events were significantly more common in travellers taking mefloquine. In all, 333 neuropsychiatric adverse events were reported by 1214 travellers taking mefloquine, compared with 189 such events in 1181 travellers taking proguanil plus chloroquine ($P < 0.001$). In all, 0.7% of travellers taking mefloquine had disabling neuropsychiatric adverse effects, compared with 0.09% of those taking proguanil plus chloroquine ($P = 0.021$). Two travellers taking mefloquine (1 in 607) were admitted to hospital as a result of the adverse event, compared with 1 in 1181 travellers taking proguanil plus chloroquine.

Conclusion—There is a significant excess of adverse neuropsychiatric events of intermediate degrees of severity associated with the use of mefloquine compared with proguanil plus chloroquine. This finding may also explain the discrepant findings between earlier studies and clinical experience.

Introduction

Malaria prophylaxis for British travellers to endemic areas includes avoiding infective mosquito bites, using chemoprophylaxis; travellers should also promptly seek treatment in the case of febrile illness.¹ Chemoprophylaxis poses the most problems because of existing drug resistance by the potentially fatal *Plasmodium falciparum*; travellers, however, are healthy people, so adverse events from antimalarial drugs are fairly unacceptable.

Between July 1993 and March 1995 the recommended chemoprophylaxis for travellers visiting areas where malaria resistant to chloroquine is widespread has been either a combination of proguanil 200 mg daily and 300 mg of chloroquine base weekly or mefloquine 250 mg weekly. During that time mefloquine was recommended for east and central Africa, mefloquine or proguanil plus chloroquine for west Africa, and proguanil plus chloroquine for the Indian subcontinent. Mefloquine has been increasingly used since it was licensed in Britain in 1990, though it is used less widely than in the United States and in some other European countries. The main concerns about mefloquine relate to reports of adverse neurological and psychiatric events. These include anxiety, depression, sleep disturbances, nightmares, hallucinations, and, in a few people, overt psychotic attacks or convulsions. The frequency of such events is unclear. Steffen *et al* reported that "serious" events occurred in around 1 in 10 000 people taking the drug² (with "serious" defined according to the restrictive definition of the Council for International Organisations of Medical Sciences as fatal, life threatening, leading to or prolonging a stay in hospital, or resulting in severe disability³), but anecdotal reports from doctors in Britain have suggested that this might be an underestimate. Because of this uncertainty about the extent of adverse side effects, we compared the adverse events associated with the use of mefloquine as antimalarial prophylaxis with those associated with the use of proguanil plus chloroquine. We specifically examined the results relating to temporarily disabling neuropsychiatric adverse events.

Subjects and methods

We retrospectively identified all travellers who had been advised between November 1993 and February 1995 via the travellers' telephone health line run by the Medical Advisory Services for Travellers Abroad to use either mefloquine or a choice of mefloquine or proguanil plus chloroquine as antimalarial prophylaxis for visiting a malarious area. We sent each traveller a postal questionnaire requesting information about any adverse events relating to antimalarial drugs taken. The questionnaire was timed to arrive after the traveller's return to Britain.

We sent all non-respondents a duplicate questionnaire four weeks later. Non-respondents to this were sent a final letter and repeat questionnaire a further four weeks later.

Respondents were included for analysis only if they had undertaken the journey that they had specified when contacting the health line and had indicated that they had taken either mefloquine or proguanil plus chloroquine.

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Grading of adverse side effects of antimalarial drugs

Grade	Side effect
1	Relatively trivial
2	Bad enough to interfere with daily activities
3	Bad enough to make traveller seek medical advice
4	Requiring hospital attention

The questionnaire sought information on antimalarial drugs taken and on compliance and specifically asked: "Did you have any side effects you would attribute to the antimalarial tablets?" The travellers were asked to grade the severity of any adverse event(s) on a scale of 1 to 4 (see box) for each of 12 specified side effects—nausea, diarrhoea, mouth ulcers, itching, headache, strange or vivid dreams, dizziness, anxiety, depression, visual difficulties, fits or seizures, and insomnia—and for a category of "any other," which they were asked to specify. They were also asked if the side effects had led them to change or stop taking the recommended antimalarial drug.

Those travellers who indicated that they had had neuropsychiatric adverse events that were severe enough to require medical advice or hospital attention were telephoned by one of the authors (PJB) for a more detailed history.

The histories obtained were presented separately to two referees (PDC and DJB) in such a way that the referees were blind to the antimalarial chemoprophylaxis that had been used. They were asked to select those travellers who had, in the opinion of each referee, experienced "disabling neuropsychiatric adverse events." Neuropsychiatric adverse events were classified according to the Committee on the Safety of Medicines' listings for neurological and psychiatric disorders, and such an event was considered disabling only when, in the opinion of both referees separately, it had prevented the traveller from undertaking the activity for which he or she had made the journey.

We analysed the results using several different measures of severity or disability: (a) by the individual affected, according to the scale presented to the travellers in the questionnaire; (b) by whether the traveller discontinued or changed prophylaxis because of the adverse effect(s); (c) by whether the traveller was admitted to hospital as a consequence of the adverse event (referees' judgment from the traveller's account); (d) by assessment of the detailed history of each traveller with neuropsychiatric adverse events and grade 3 or 4 in terms of disability. Hospital admission was the only criterion used in the earlier, large scale study.³

We also present brief summary histories of travellers with neuropsychiatric adverse events of grade 3 or 4 that were, in the referees' opinions, temporarily disabling.

We believe that this is the minimum information required to meet the need for clarity and to facilitate comparison with other published data. Data were analysed using Epi-Info software.

Results

In all, 4953 questionnaires were sent out, of which 3851 were returned and available for analysis (response rate 77.8%). Of the 3851 travellers who returned their questionnaire, 3375 (87.6%) had undertaken the journey that they had described when contacting the health line. Of those undertaking the described journey, 2560 (75.9%) took antimalarial chemoprophylaxis, with 2395 of these taking mefloquine or proguanil plus chloroquine (1214 mefloquine, 1181 proguanil plus chloroquine). Of the 1102 non-respondents, 792 had been advised to take mefloquine and 310 to take proguanil plus chloroquine as the first antimalarial drug of choice.

Thus, during the 16 months of the study 2395 travellers were eligible for the study; 50.7% (1214) of the subjects took mefloquine and 49.3% (1181) took proguanil plus chloroquine. A small majority (54.2% (602/1111)) of travellers used proguanil plus chloroquine in the first half of the study and a similar proportion (54.9% (705/1284)) used mefloquine in the second half, owing to changing recommendations.

The proportion of female travellers in the group that took mefloquine was 57.5% (698/1214) and in the group that took proguanil plus chloroquine was 58.7% (693/1181). The age distribution was similar in each group.

The duration of antimalarial use was similar for the two regimens. Both regimens were used for a median of seven weeks.

As expected, the antimalarial drug taken depended on the destination, according to the recommendations on prophylaxis for different parts of the world. Most of those advised to take mefloquine travelled to east Africa or South East Asia, while most of those advised to take proguanil plus chloroquine were visiting other parts of Africa or Latin America.

When analysing the incidence of adverse events relating to a particular regimen we calculated the rates by including only respondents (mefloquine $n = 1214$, proguanil plus chloroquine $n = 1181$) in the denominator. While this is statistically correct and the experiences of non-respondents should not be predicted, we recognise the argument that those experiencing adverse events are more likely to respond in a study of this nature. In contentious areas we have therefore also calculated the results by including those who were advised to take the relevant regimen but did not return the questionnaire (mefloquine $n = 2006$, proguanil plus chloroquine $n = 1491$).

SELF REPORTING

Table 1 shows the numbers of respondents reporting gastrointestinal, neuropsychiatric, or other adverse

Table 1—Numbers (percentages) of travellers reporting gastrointestinal, neuropsychiatric, or other adverse events while taking mefloquine ($n = 1214$) or chloroquine and proguanil ($n = 1181$), by four grades of severity

Grade	Gastrointestinal		Neuropsychiatric		Other		Any adverse event	
	Mefloquine	Chloroquine + proguanil	Mefloquine	Chloroquine + proguanil	Mefloquine	Chloroquine + proguanil	Mefloquine	Chloroquine + proguanil
1	152 (12.5)	193 (16.3)	190 (15.7)	119 (10.1)	73 (6.0)	86 (7.3)	293 (24.1)	291 (24.6)
2	88 (7.2)	100 (8.5)	112 (9.2)	58 (4.9)	42 (3.5)	41 (3.5)	158 (13.0)	149 (12.6)
3	24 (2.0)	14 (1.2)	27 (2.2)	11 (0.9)	17 (1.4)	16 (1.4)	46 (3.8)	34 (2.9)
4	2 (0.2)	2 (0.2)	4 (0.3)	1 (0.1)	3 (0.2)	3 (0.3)	6 (0.5)	5 (0.4)
All grades	266 (22)	309 (26)	333 (27)	189 (16.0)	135 (11.1)	146 (12.4)	503 (41.4)	479 (40.6)

Some respondents had side effects in more than one category of adverse event.

events by grade of perceived severity and by antimalarial drug taken. Overall, an equal proportion of respondents reported experiencing some kind of adverse event with either regimen (41% (503/1214) taking mefloquine, 40.6% (479/1181) taking proguanil plus chloroquine), and there was no significant difference at any grade of severity. A significantly greater proportion of individuals taking proguanil plus chloroquine had gastrointestinal side effects than those taking mefloquine ($P = 0.02$). When the results were examined by grade of severity, however, the difference was only significant at grade 1 ($P = 0.009$). A greater proportion of mefloquine users reported gastrointestinal side effects of grade 3 than did users of proguanil plus chloroquine.

A significantly greater proportion of mefloquine users reported neuropsychiatric side effects (overall $P < 0.001$) at all grades except grade 4 (grade 1 and 2, $P < 0.001$; grade 3, $P = 0.02$). Among the other adverse events, mouth ulcers were reported by 4.3% (51/1181) of those taking proguanil plus chloroquine and 2.1% (25/1214) of those taking mefloquine. In all, 1.9% (22/1181) of those taking proguanil plus chloroquine and 0.7% (8/1214) taking mefloquine considered the ulcers to be grade 2 severity or above. Both differences were significant ($P < 0.002$ and $P < 0.01$ respectively). There was no difference between the proportion of respondents reporting other side effects at any grade.

EFFECT OF ADVERSE EVENTS ON ADHERENCE TO CHEMOPROPHYLAXIS

Among the respondents who stated that they had had an adverse event, 0.7% (8/1214) of the mefloquine users said that this had led them to change their antimalarial chemoprophylaxis and 5.1% (63/1214) said that they had stopped taking chemoprophylaxis. The corresponding figures for proguanil plus chloroquine were 0.3% (3/1181) and 6.3% (74/1181), which were not significantly different from those for mefloquine.

ADMISSION TO HOSPITAL

Six respondents taking mefloquine who were admitted to hospital reported adverse events of grade 4. We were unable to follow up one subject who complained of strange or vivid dreams. One subject's admission (for pneumonia) was considered to be unre-

lated to use of mefloquine, and one subject had misinterpreted the questionnaire and had not been admitted. The remaining three subjects had been admitted to or been treated in hospital as a result of adverse events while using mefloquine. One subject had been treated as a psychiatric outpatient, one had been admitted for investigation, and one had been admitted for a short time before returning home.

Five respondents who were admitted to hospital taking proguanil plus chloroquine reported adverse events of grade 4. One subject complaining of visual difficulties was lost to follow up. One subject's admission (for dysentery) was considered to be unrelated to use of proguanil plus chloroquine, and one respondent had misinterpreted the questionnaire and had not been admitted. The referees thought that hospital admission for one subject had been inappropriate (she had developed a minor rash while abroad). The remaining subject had been investigated in hospital as a result of adverse effects associated with the use of proguanil plus chloroquine. This person was observed on two occasions to be fitting while asleep. On return to Britain she was investigated as an outpatient. On the basis of the criteria used in the earlier large scale survey,² therefore, two people taking mefloquine and one taking chloroquine plus proguanil had been admitted to hospital owing to "serious" adverse effects.

TRAVELLERS WITH GRADE 3 OR 4 NEUROPSYCHIATRIC ADVERSE EVENTS

Forty three respondents reported neuropsychiatric side effects of grade 3 or 4, of whom 31 had taken mefloquine and 12 proguanil plus chloroquine.

Of the mefloquine users, two users were lost to follow up, and in five cases the referees considered that the side effects were unrelated to the use of mefloquine or were not neuropsychiatric in nature. Ten respondents had had disabling neuropsychiatric side effects associated with the use of mefloquine (table 2), and an additional 14 had had unpleasant but not disabling neuropsychiatric side effects. One of those assessed as having had disabling neuropsychiatric side effects reported a strong family history of epilepsy that should have been regarded as a contraindication against the use of mefloquine. This case was excluded from further analysis. Two of the respondents with unpleasant neuropsychiatric side effects had previously been treated for depression and were also excluded.

Table 2—Summary data on travellers who had disabling neuropsychiatric adverse events associated with the use of mefloquine or chloroquine

Sex	Date of birth	Summary	Relevant medical history	Medical advice	Hospital treatment	Stopped tablet
Mefloquine						
Female	17 Jun 1973	Hallucinations, panic attacks, dissociation from reality, difficulty walking; repatriated	Mild pre-examination panic attacks four years before	Yes	Yes, psychiatric outpatient	Yes
Female	Not known	Confusion, difficulty concentrating, dizziness; unable to work effectively; made mistakes	None	Yes	No	No, advised to continue
Male	7 Aug 1945	Depression, anxiety, panic attacks, hallucinations; unable to work; repatriated	None	Yes	Yes, admitted before repatriation	Yes
Female	20 Apr 1973	Emotional instability, depression, anxiety, personality changes	None	Yes	No	Yes
Female	6 Jun 1964	Dizziness, disorientation, dissociation from reality; unable to work	None	Yes	No	Yes
Female	25 Mar 1963	Lack of concentration, dissociation from reality, headache, difficulty walking	None	Yes	No	Yes
Female	25 Feb 1971	Loss of consciousness; grand mal seizure witnessed by nurse	Family history of epilepsy	Yes	Yes, admitted for investigation	Yes
Female	7 May 1965	Unpleasant nightmares, dizziness, difficulty focusing, fear and inability to go out unaided	None	Yes	No	No, advised to continue
Male	27 Oct 1938	Severe dizziness leading to vomiting; bedridden for 48 hours	None	Yes	No	Yes
Female	4 Aug 1957	Dissociation from reality, headache, feeling faint, anxiety, depression	None	Yes	Yes, admitted for investigation	No
Chloroquine and proguanil						
Female	11 Jun 1973	Seen to have two seizures while asleep	None	Yes	Yes, admitted for investigation after return to Britain	Yes

Key messages

- Uncertainty persists about the frequency of adverse neurological and psychiatric events associated with the antimalarial drugs mefloquine and proguanil plus chloroquine
- This study shows that about 40% of travellers taking either mefloquine or chloroquine and proguanil can expect to experience some sort of adverse side effect, although most side effects will be relatively trivial
- About 0.7% (1 in 140) travellers taking mefloquine can expect to have a neuropsychiatric adverse event unpleasant enough to temporarily prevent them from carrying out their day to day activities, compared with 0.09% (1 in 1100) taking chloroquine and proguanil
- Mefloquine is appropriate only when the risk is high both of malaria and of chloroquine resistance

Thus nine (0.7%) subjects had disabling neuropsychiatric side effects after taking mefloquine. Overall, 21 (1.7%) subjects had unpleasant or disabling neuropsychiatric side effects of any grade after taking mefloquine.

Among the 12 users of proguanil plus chloroquine, one was lost to follow up, and, in six cases, the referees agreed that the side effects were unrelated to the use of proguanil plus chloroquine or were not neuropsychiatric in nature. One respondent (0.09%) was deemed to have had a disabling neuropsychiatric side effect associated with the use of proguanil plus chloroquine (table 2), and an additional four were considered to have had unpleasant but not disabling neuropsychiatric side effects (overall, 0.4%). The rates for disabling ($P = 0.02$) and combined ($P = 0.004$) neuropsychiatric side effects differed significantly between the two regimens, but the rates for unpleasant effects did not ($P = 0.09$).

If we take as the denominator the number of non-respondents advised to take each regimen then 0.5% (9/2006) of those advised to take mefloquine and 0.07% (1/1491) of those advised to take proguanil plus chloroquine had disabling neuropsychiatric side effects ($P = 0.05$). Unpleasant but not disabling neuropsychiatric side effects were experienced by 0.6% (12) of those advised to take mefloquine and by 0.3% (4) of those advised to take proguanil plus chloroquine ($P = 0.2$). Overall, 1.1% (21) of those advised to take mefloquine and 0.3% (5) of those advised to take proguanil plus chloroquine had either unpleasant or disabling neuropsychiatric side effects ($P = 0.03$).

Discussion

The results show how relative frequencies of adverse events vary, depending on the criteria used. The frequency of discontinuing or changing chemoprophylaxis was the same for proguanil plus chloroquine and mefloquine. The frequency of "serious" adverse events (as defined by the criteria of the Council for

International Organisations of Medical Sciences) that were apparently related to chemoprophylaxis was one case for proguanil plus chloroquine and two for mefloquine, each in a population of around 2300. Though these rates are suggestive of rates higher than 1 in 10 000, the study is too small to generate accurate data on rates of very rare events.

The most prominent differences in self reported adverse events between the two regimens are in the neuropsychiatric category, where adverse events with mefloquine categorised by the traveller as "bad enough to interfere with daily activities" (9.2% of users) or "bad enough to make you seek medical advice" (2.2%) were each about twice as common as with proguanil plus chloroquine. Overall, 11.8% of people taking mefloquine had adverse neuropsychiatric events of grade 2 or worse. When histories were taken from respondents with self reported grades 3 and 4 and evaluated, nine people (0.7%) taking mefloquine and one person (0.09%) taking proguanil plus chloroquine had temporarily disabling neuropsychiatric symptoms.

It therefore seems that, although the proportion of people abandoning the regimen is the same for mefloquine and proguanil plus chloroquine, and "serious" side effects are rare with each, there is a significantly raised frequency of neuropsychiatric side effects in those taking mefloquine. It seems that these side effects are experienced as disabling or very upsetting by those affected. These observations provide an explanation for the discrepancy in results from published surveys and reported clinical anecdotes.

This study concentrated on one group of adverse events in an attempt to shed light on a specific issue. It did not cover every aspect of adverse events in the same detail nor has it examined prophylactic efficacy—for which larger populations would be needed—and therefore addresses only one aspect of the choice of regimens for travellers. The findings of this study are, however, consistent with clinical impressions in Britain and will tend to favour the view that mefloquine is appropriate only where the risk is high both of malaria and of chloroquine resistance.

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Adverse local reactions from accidental BCG overdose in infants

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Local reactions to BCG vaccine depend on the administration technique, the dose, and the type of BCG preparation.¹ We report on infants who were accidentally vaccinated intradermally with a percutaneous

BCG preparation, receiving about five times the upper limit of the currently recommended intradermal dose of BCG.

Methods and results

All infants born at our hospital before November 1994 were routinely given intradermal BCG after written parental consent was obtained. A total of 857 infants were accidentally vaccinated intradermally with the percutaneous BCG (Evans E4981A and E4946B) between July and November 1994. After public announcement of the error, 556 of these infants attended special follow up clinics where they were examined for adverse reactions to BCG.

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