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Acute and long-term psychiatric side effects of mefloquine: A follow-up on Danish adverse event reports

Q4 Åsa Ringqvist [a,b,*], Per Bech [c,d], Birte Glenthøj [d,e], Eskild Petersen [f]

[a] Department of Health Sciences, Lund University, Lund, Sweden
[b] Department of Rehabilitation Medicine, Skane University Hospital, Lund, Sweden
[c] Psychiatric Center North Sealand, Psychiatric Research Unit, Hillerød, Denmark
[d] Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[e] Center for Neuropsychiatric Schizophrenia Research & Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Copenhagen University Hospital, Psychiatric Center Glostrup, Denmark
[f] Department of Infectious Diseases, Aarhus University Hospital Skejby, Aarhus, Denmark

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Summary *Background:* The aim of the study was to explore the profile of acute and long-term psychiatric side effects associated with mefloquine.
Methods: Subjects ($n = 73$) reported to a Danish national register during five consecutive years for mefloquine associated side effects were included. Acute psychiatric side effects were retrospectively assessed using the SCL-90-R and questions based on Present State Examination (PSE). Subjects reporting suspected psychotic states were contacted for a personal PSE interview. Electronic records of psychiatric hospitalizations and diagnoses were cross-checked. Long-term effects were evaluated with SF-36. SCL-90-R and SF-36 data were compared to age- and gender matched controls.
Results: In the SCL-90-R, clinically significant scores for anxiety, phobic anxiety and depression were found in 55%, 51%, and 44% of the mefloquine group. Substantial acute phase psychotic symptoms were found in 15% and were time-limited. Illusions/hallucinations were more frequently observed among women. Cases of hypomania/mania in the acute phase were 5.5%. Significant long-term mental health effects were demonstrated for the SF-36 subscales mental health (MH), role emotional (RE), and vitality (VT) in the mefloquine group compared to matched controls.

* Corresponding author. Department of Rehabilitation Medicine, Lasarettsgatan 13, Skane University Hospital, 221 85 Lund, Sweden. Tel.: +46 46 171635, +46 70 4415889; fax: +46 46 134837.
E-mail address: asa.ringqvist@med.lu.se (Å. Ringqvist).

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Conclusion: The most frequent acute psychiatric problems were anxiety, depression, and psychotic symptoms. Data indicated that subjects experiencing acute mefloquine adverse side effects may develop long-term mental health problems with a decreased sense of global quality of life with lack of energy, nervousness, and depression.

1. Background

Mefloquine is a cost effective drug for prophylaxis and treatment of *Plasmodium falciparum* malaria and has been available as a chemoprophylaxis since 1985 [1,2]. Initial clinical trials indicated that side effects were mild [3–5], and serious adverse events were rarely observed [6]. A double-blinded, randomized study compared adverse reactions between mefloquine and other anti-malaria prophylaxis regimes and did not find a significant difference between the different anti-malarials [7]. It did, however, find more neuropsychiatric adverse events in women. Other studies have been somewhat contradictory and in a Cochrane report 2009 it was concluded that mefloquine had more neuropsychiatric adverse events than atovaquone/proguanil and doxycyclin even though the quality of the available evidence was poor [8]. Risk factors for the occurrence of neuropsychiatric adverse events in response to mefloquine have been established and are, apart from the female sex, personal or family history of seizures or affective disorder [9].

As to the profile of psychiatric adverse events, database research have reported that mefloquine may increase the risk of psychosis and anxiety reactions, but not the risk of first time diagnosis of depression [10]. Schneider et al. did not find substantial evidence that neuropsychiatric disorders are associated with mefloquine, with the exception of acute psychosis [11].

Although it is not clear that mefloquine-correlated neuropsychiatric adverse events exceeds what is seen with other antimalarials, it is still a clinical problem. Reviews of mefloquine have pointed to the need for studies designed to explore the neuropsychiatric adverse profile of mefloquine [9,2]. So far Profile of Mood (POMS) questionnaire has been used to compare neuropsychiatric side effects [7,12–14].

In this study we combined two well-known validated questionnaires with questions derived from a structured psychiatric interviewing instrument to evaluate psychiatric symptoms and current mental health in subjects reported for mefloquine adverse side effects to a Danish national register. We also performed crosschecking of electronic records of psychiatric hospitalizations.

2. Methods

2.1. Study population

The Danish National Drug Authority, Committee of Adverse Drug Reactions, gave access to all reports of adverse events associated with mefloquine received between January 1.1996 and August 1.2000, 95 reports in all (see Fig. 1). With one exception, written consent to contact each case were obtained from the physicians who had been reporting the side effects. One person had been reported twice, thus 93 cases were considered for inclusion in the study. Four persons were under the age of 18, and were excluded in the study for ethical reasons. Two subjects had died and one subject had emigrated. One report was a mistake and the subject had not used mefloquine. Thus, the questionnaire was sent to the remaining 85 persons, out of whom 76 responded, ensuring a response rate of 89%.

Three subjects were excluded from the analyses after reviewing their questionnaires; two reported commencement of symptoms more than three months after termination of mefloquine use (defined as an exclusion criterion) and one person, who had developed idiopathic thrombocytopenia, was concurrently treated with corticosteroids. A total of 73 questionnaires were included in the analysis.

Cases with previous personal or family history of psychiatric illness were identified by the questionnaire, and by cross-checking with the Danish psychiatric nationwide case register.

2.2. Questionnaire

The questionnaire was divided into 6 sections:

2.2.1. Background questions

Background questions included gender, age, body weight, travel destination, duration of travel, duration of mefloquine use and onset of symptoms, chronic illness, previous CNS-events, previous psychological problems and family history of psychiatric disease.

2.2.2. Checklist of common physical symptoms

Checklist of common physical symptoms (including neurologic symptoms) frequently reported historically in response to mefloquine were included.

2.2.3. Symptoms checklist-90-revised (SCL-90-R)

SCL-90-R is a 90-item self-report symptom inventory designed to reflect the psychological patterns of community, medical, and psychiatric respondents (for detail see Suppl. information) [15,16]. The SCL-90-R was altered to retrospectively obtain an estimation of the general symptom level (Global Severity Index, GSI) as well as to assess nine primary symptoms dimensions of psychological distress during the acute phase of the adverse event. Psychometric properties of SCL-90-R has been investigated [17]. The raw score cut-offs for caseness were based on Danish data [18].

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Also, the age- and gender matched Danish controls originated from this population.

2.2.4. Present state examination (PSE)

Item response model analysis of the SCL-90-R subscales for psychotism, paranoid ideation and hostility were in a study noted to function less well than the other, "neurotic", subscales [19]. Therefor suspected psychotic symptoms were investigated by including relevant PSE questions [20,21] in the questionnaire. See Suppl. information for more detail on PSE. ICD-10 research criteria were used to evaluate the plausibility of a hypomanic/manic case.

2.2.5. Consequences of the adverse events

The subjects were asked about nightmares, drug use, and consequences of the adverse events such as hospitalizations. Additionally, medication or other treatments the subjects had received when experiencing the adverse events were recorded.

2.2.6. Short-Form-36 questions (SF36)

Finally, subjects' perception of current general and mental health was explored using four subscales from Short-Form-36 (SF-36) [22,23]. The control group of age- and gender matched subjects was derived from a Danish population previously described [24]. The psychometric properties of the Danish SF-36 has been investigated [25].

2.3. Pilot

See Suppl. information.

2.4. Procedure

If the questionnaire was not returned within three weeks after being mailed, a reminder was sent out. Hereafter no further attempt was made to contact those who had not responded. The questionnaire was active 28th September – 27th November 2000.

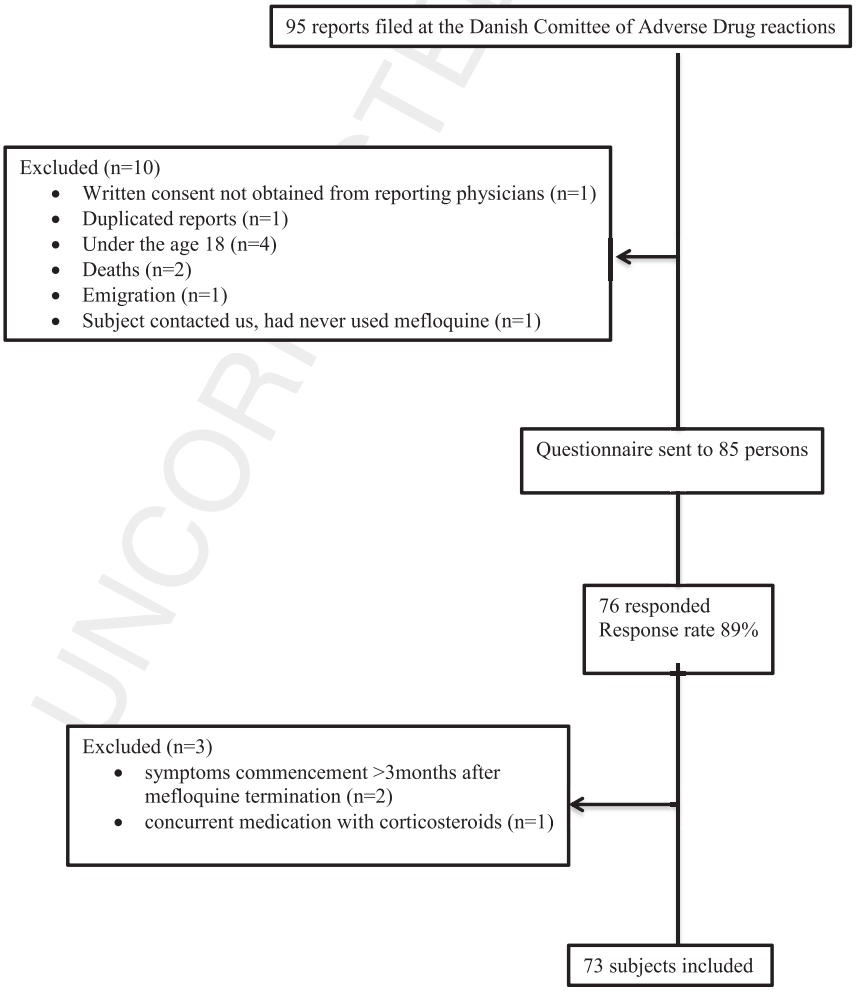

Fig. 1 Flow chart demonstrating the process from 95 initial reports to the Danish Comittee of Adverse Drug reactions to the 73 subjects included in the study.

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2.5. Telephone interviews

Structured telephone interviews (using PSE) were carried out with 13 subjects (see Suppl. information).

2.6. Danish psychiatric nationwide case register

The Danish psychiatric nationwide case register was consulted for hospital admissions pre- and posts the adverse events.

2.7. Ethical clearance

Scientific ethical clearance was obtained from the Scientific Ethical Committee of Copenhagen Municipality (Ref. no. KF01-144/00). Permission to register the data was obtained from the Danish Data Protection Agency.

2.8. Data analysis

Between-group differences within the mefloquine group (e.g. with respect to gender, history of mental illness etc.) were analyzed using the Chi-squared test. The Mann–Whitney non-parametric analysis was used to test the differences of the SCL-90-R and SF-36 scores between the adverse event group and the age- and gender matched control groups. A value of $p < 0.05$ was regarded as statistically significant. Data are presented as mean ± standard deviation (SD).

3. Results

3.1. The initial adverse events reports

The 73 initial reports of mefloquine adverse event reports filed to The Danish National Drug Authority, Committee of Adverse Drug Reactions included the following complaints; 45 subjects reported physical symptoms (including neurological), 27 concerned signs of anxiety ("neurosis" was coded as anxiety), 26 reported sleep disturbances (including nightmares), 18 dealt with depression/feeling low, 11 reports concerned signs of a possible psychotic states (delusions/hallucinations), cognitive problems were described in nine reports, three reported confusion, and one mania. More than one complaint was described in 40 reports.

Table 1 Number of prescribed doses of mefloquine, number of adverse events (AE) reported to the Danish Drug safety register and reported AE per doses prescribed each year. Data derived from the Danish National Prescription Database (http://www.ssi.dk/Sundhedsdataogit/Registre%20og%20kliniske%20databaser/De%20nationale%20sundhedsregistre/Sygdomme%20leagemidler%20behandlinger/Laegemiddelstatistikregisteret.aspx).

	No. of doses ('000)	Reported AE	Reported AE per doses ('000)
1996	109.6	14	1:7.83
1997	156.0	14	1:11.14
1998	133.6	26	1:5.14
1999	76.8	29	1:2.65
2000[a]	28.0	12	1:2.33

[a] Up to 31 July.

3.2. Number of prescribed doses of mefloquine 1996–2000

For number of prescribed doses of mefloquine, number of adverse events (AE) reported to the Danish Drug safety register and reported AE per doses prescribed each year 1996–2000 see Table 1.

3.3. Response rate

The response rate of the questionnaire was 89% (see method).

3.4. Background data

The time span from onset of the adverse events to filling out the questionnaires ranged from 270 to 2010 days; mean 988 ± 429 days. Of the 73 cases, 49 had traveled to Africa and 23 to Asia. Six women, but no men, reported previous CNS-events including five cases of migraine and one case of concussion. With the exception of previous CNS-events, there was no statistical difference in the distribution of the above-mentioned data with respect to sex, previous psychiatric problems or family history of psychiatric problems.

Of the 73 subjects, 78% reported no previous personal, nor family history of psychological/psychiatric problems, 8% reported a family (but no personal) history of psychiatric/psychological problems, and 13% (10 subjects) reported that they had previously been treated by a physician and/or psychotherapist for mental health problems. Cross-checking with the Danish psychiatric nationwide case register revealed that three in this latter group, but none of the other subjects, had previously been admitted to an in-hospital psychiatric facility.

Mefloquine was prescribed as malaria chemoprophylaxis to 67 of the 73 subjects and for treatment in six cases. The majority i.e. 77%, had their symptoms debut within the first three weeks of treatment, 15% experienced debut of symptoms between the first and second month of treatment and 8% reported commencement of symptoms later than 8 weeks after the start of mefloquine intake.

Two subjects reported having tried narcotic drugs during traveling, one had tried opium, and yet another subject had tried marijuana. These two subjects were not part of the group experiencing psychotic symptoms. The distribution of age, weight and height of the study subjects are presented in Table 2.

3.5. Acute adverse side effects

3.5.1. Physical symptoms

Results are shown in Table 3.

3.5.2. Anxiety and depression

The SCL-90-R results displayed significantly ($p < 0.01$) higher scores for the validated subscales anxiety, phobic

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Table 2 The distribution of age, weight and height in a group of 73 cases with adverse reactions to mefloquine who were reported to the Danish Committee of Adverse Drug Reactions in the period 1st January 1996 to 7th of August 2000. Q3

	Men $n = 33$		Women $n = 40$	
	No previous personal, and/or family history of psychiatric disorder $N = 26$	Previous personal, and/or family history of psychiatric disorder $N = 7$	No previous personal, and/or family history of psychiatric disorder $N = 31$	Previous personal, and/or family history of psychiatric disorder $N = 9$
Age (Years (range) ± SD)	41 (24–76) ± 14.2	49 (29–71) ± 15.4	41 (22–75) ± 14.0	39 (20–62) ± 14.9
Weight (kg ± SD)	81 ± 7.6	84 ± 8.5	64 ± 8.4	59 ± 8.0
Height (cm ± SD)	181 ± 6.3	184 ± 8.0	167 ± 7.7	168 ± 3.0

anxiety, and depression in the adverse event group compared to the matched Danish control group (Table 4). In the same subscales, i.e. anxiety, phobic anxiety, and depression, 55%, 51%, and 44% of the study subjects had scores above Danish cut-offs for caseness (i.e. clinically significant). The subjects estimation of duration of symptoms indicated in the SCL-90-R are given in Table 5. Out of 73 subjects, 30 subjects reported symptoms lasting more than 9 months.

3.5.3. Hypomanic/manic states

Only 4 of the 73 subjects (5.5%) indicated that they had experienced hypomanic/manic states in the PSE questions and three of these were judged to be possible clinical cases. In addition, one subject who had not indicated hypomanic/manic symptoms in the questionnaire was admitted to a psychiatric in-hospital care under the diagnosis "mania without psychotic symptoms". Thus, after evaluation, we identified four (5.5%) possible cases of hypomania/mania (see Suppl. information).

3.5.4. Psychotic states

Perceptual disturbances/hallucinations and/or delusional experiences were rated positive in the PSE questions by 17 subjects (23%) out of which nine women and eight men. There was an overlap between many of the subjects experiencing both perceptual disturbances/hallucinations and delusional mood/delusions.

Six of the subjects had described less severe symptoms. They had indicated gustatory or olfactory sensations, hypnopompic (in connection to waking up) and/or hypnogogic (in connection to falling asleep) perceptual disturbances and/or delusional mood, respectively. Eleven subjects (15%) were considered to have a more severe set of symptoms and contact was sought for a personal PSE interview by phone, see method. The results are presented below.

Visual or auditory illusions/hallucinations were described by seven subjects (10%). Four subjects reported a combination of visual and auditory illusions/hallucinations with a duration of 1–2 days, 3–13 days, 2–3 weeks and 2–3

Table 3 Physical symptoms in association with mefloquine exposure in a group ($n = 73$) experiencing adverse reactions to mefloquine.

Physical complaint	Percentage of total ($n = 73$) indicating symptoms
Gastrointestinal symptoms	57%
Dizziness	57%
Fatigue	49%
Abnormal vision	49%,
Palpitations	42%
Vertigo	38%
Headache	36%
Skin symptoms	36%
Numbness of arms and legs	30%
Tinnitus	18%
Fever	16%
Leg cramps	14%
Loss of hair	12%
Hearing loss	12%
Reduced nociception of the skin	10%
Involontary movements	10%

Table 4 The SCL-90-R retrospective scores of 73 cases with adverse reactions to mefloquine compared to Danish norms matched for age and gender ($N = 1090$). Each item was rated on a five-point scale of distress (0–4) ranging from "not at All" through "Extremely".

	Adverse event group ($n = 73$)	Danish norms ($n = 1090$)	P
Somatization	0.90 ± 0.71	0.49 ± 0.53	<0.01
Obsessive-compulsive	1.08 ± 0.95	0.62 ± 0.60	<0.01
Interpersonal sensitivity	0.66 ± 0.80	0.55 ± 0.57	n.s.
Depression	1.18 ± 1.00	0.59 ± 0.64	<0.01
Anxiety	1.39 ± 1.03	0.40 ± 0.47	<0.01
Anger-hostility	0.51 ± 0.7	0.34 ± 0.41	n.s.
Phobia	0.77 ± 1.04	0.13 ± 0.33	<0.01
Paranoid ideation	0.4 ± 0.63	0.47 ± 0.59	<0.05
Psychotism	0.47 ± 0.51	0.22 ± 0.32	<0.01
Total SCL-90-R	2.09 ± 0.68	0.45 ± 0.43	<0.01

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Table 5 Subjects' estimation of duration of physical symptoms, nightmares, cognitive dysfunction, and symptoms in response to mefloquine in the SCL-90-R. The study population consisted of 73 cases reported for adverse side effects to mefloquine.

	Cases indicating symptoms	1–2 days	3 days – 3 weeks	1–3 months	4–8 months	9 months – 3 years	Still symptoms
Nightmares	43	2	11	12	5	4	9
Cognitive dysfunction	42	2	10	7	3	6	14
SCL-90-R	68	2	18	12	6	13	17

months, respectively. One subject reported visual hallucination with a duration of 2–3 months, and finally two subjects described auditory hallucinations that had lasted for 2–3 weeks. Six of the seven cases describing illusions/hallucinations (visual and/or auditory) were women.

Delusional mood and delusions of reference in combination were experienced by seven subjects (10%). In addition, 4 subjects (5%) described delusional mood. The duration of these symptoms were 1–2 days for one, 3–13 days for two, 2–3 weeks for two, 2–3 months for one, and 9–11 months for one subject. The distribution of women: men were 4:3.

Only one of the subjects of the subjects describing a possible psychotic state had previously been admitted to any Danish psychiatric in-patient care prior to the adverse event (see Suppl. information).

3.5.5. Nightmares and cognitive problems

Recurring nightmares in response to mefloquine intake were reported by 59% of the study subjects, and 59% of the subjects stated cognitive problems (see Suppl. information). Duration of nightmares and cognitive dysfunction are given in Table 5.

3.6. Consequences and treatments of the adverse events

In all, 41% of the study subjects reported that they had obtained some treatment for their perceived psychiatric adverse event.

3.6.1. Hospitalizations

Four (5.4%) of the study population were hospitalized due to physical side effects and 10 subjects (14%) due to psychiatric symptoms. Out of the 10 individuals receiving in-hospital psychiatric care, eight (10%) had reported perceptual disturbances/hallucinations and/or delusional experiences/delusional mood. Thus, psychotic states were the most common reason to receive in-hospital psychiatric care. For detail see Suppl. information.

3.6.2. Psychopharmacological treatments

Twenty-two subjects (32%) had been prescribed psychopharmacological medication. Antidepressive drugs were prescribed to 15% of the mefloquine group and 7% were prescribed antipsychotic drugs. Sedatives were prescribed to 12% of the subjects as the single psychopharmacologic treatment and also used in some of the above cases in addition to antidepressive- or antipsychotic drugs. 22% of the study population received psychotherapeutic treatment. For detail see Supplementary information.

3.7. Long-term effects

The SF-36 scores, reflecting current perception of health (mean 988 ± 429 days after the acute symptoms) of the 73 subjects were compared to a Danish control group ($N = 3923$) matched with respect to age and gender and showed significantly poorer mental health scores, see Table 6.

The results of the 73 cases were tested to see if there were any between-group differences considering the groups 1) No previous personal or family history of psychiatric disorder, 2) Previous personal history of psychiatric disorder, and 3) No previous personal but family history of psychiatric disorder. For this purpose the SF-36 results for each dimension were divided into quartiles of the normal distribution. No statistical between group difference was detected.

4. Discussion

This is the first larger comparative study of long term psychiatric outcome following mefloquine associated adverse events. Using the SF-36, we found significantly poorer

Table 6 The SF-36 scores reflecting perception of current general and mental health of 73 cases with adverse reactions to mefloquine compared to Danish norms matched for age and gender ($N = 3923$). In the SF-36, subjects were asked questions related to how well they had been coping the last four weeks. The scores were subsequently transformed in a standardized way into a 0-100 scale where higher scores indicate better general and mental health (Role emotional defines to what extent emotional discomfort has restricted working capacity or other activities).

	Adverse event group ($n = 73$)	Danish norms matched for age and gender ($n = 3923$)	P
General health (GH)	76.77 ± 20.89	76.16 ± 20.06	n.s.
Vitality (VT)	60.07 ± 25.62	69.84 ± 19.96	<0.01
Role emotional (RE)	73.97 ± 36.11	86.33 ± 27.63	<0.01
Mental health (MH)	74.03 ± 18.21	81.77 ± 15.51	<0.01

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results for the subscales vitality (VT), role emotional (RE), and mental health (MH) in the mefloquine group compared to a matched control population. Also, 30 out of the 73 subjects reported that the symptoms of mental problems they had indicated in SCL-90-R lasted more than 9 months. These results imply a risk for long-term reduced mental health following acute adverse side effects to mefloquine.

In a previous validation study [26], self-reported nervousness and depression were closely associated with MH, and MH could predict global quality of life. VT was strongly correlated with general fatigue and RE moderately correlated with self-reported nervousness and depression. Judging from these data, the results of the SF-36 points to a long-term decreased sense of global quality of life, increased feelings of nervousness, depression, and fatigue in the adverse event group. On the other hand, the absence of difference between the mefloquine group and matched controls in the subscale general health (GH) suggests no long-term effects on perception of physical health.

Previous studies have investigated the possibility of mefloquine having neurotoxic properties. Results have suggested neuronal oxidative damage and subsequent apoptosis mediated neurodegeneration [27,28]. These results based on animal studies are naturally not directly applicable to human subjects and must be interpreted with care. It is recognized that stressful life events are associated with the origins of depression and anxiety [29–32]. Many had multiple psychiatric, neurological and other physical symptoms. A majority (59%) of the study group also experienced cognitive impairment and deficient sleep with nightmares, respectively. These symptoms lasted for the majority more than a month. One could hypothesize that the adverse events signified a stressful life event of some impact, which could increase the risk of long-term reduced mental health.

When looking into the most frequent psychiatric acute side effects to mefloquine, clinically significant scores were demonstrated for the validated subscales anxiety, phobic anxiety and depression in 55%, 51%, and 44% of the study subjects (As a comparison, 57% of the study subjects indicated gastrointestinal symptoms and dizziness). It should be noted that we used Danish cut-offs for determining whether anxiety, phobic anxiety and depression were clinically significant. These cut-offs were considerably higher than those reported for a US sample and were derived from a non-patient population where 17.5% were classified as cases [18]. Compared to the control group, the scores of the mefloquine group for the subscales anxiety, phobic anxiety and depression were also significantly higher.

Perceptual disturbances/hallucinations and delusions were seen in 23% of the cases and in 15% they were judged to be substantial. Fortunately these symptoms were time-limited. It was notable that six out of seven subjects experiencing visual and/or auditory hallucinations/illusions were women. The differences in ratios of perceptual disturbances women vs. men could possibly imply either an increased susceptibility to mefloquine in women and/or an effect dose-dependent effect of mefloquine due to lower BMI in women.

Four (5.5%) subjects were identified as hypomanic/manic cases and out of these two were hospitalized. Thus, manic states seem to be an infrequent adverse event, but may have been underestimated. In manic states the issue of insight is problematic. Also, if a depressive episode follows the manic/hypomanic state, which is common, the subject is prone to remember the depressive episode more clearly.

Seven percent of the study population were prescribed antipsychotic medication, which can be used to treat psychotic as well as manic states. Clinically, antipsychotic treatments in Denmark have usually not been prescribed within the first days of admission. Instead there has been a tradition to start treatment with sedatives. The seven cases treated with antipsychotic medication are consequently a rather robust estimate of more severe and pervasive psychotic or manic states.

The present data must obviously be considered with care. The acute effects are assessed retrospectively in the questionnaire and one must consider the risk of memory bias. However, the results of the initial reports, the given spectrum of treatments supplied to the mefloquine group, and data from the Danish psychiatric nationwide case register do not seem to contradict the results. One of the strength in this investigation is a high response rate of 89%, but the study subjects were not randomly selected. It is likely that our study population represent the more serious end of the adverse event scale both concerning physical and psychiatric symptoms. It could however, be assumed that our study population provides a comprehensive picture of the panorama of the more serious psychiatric adverse events.

One aspect to consider is whether our study group of individuals reported for mefloquine associated adverse events could be more susceptible to psychiatric acute adverse event and long-term mental health problems. This was taken under considerations both in the questionnaire and by cross-checking of psychiatric hospitalizations. Compared to a random population, 13% does not signify an overrepresentation in the general population of individuals with a history of previous episodes of mental problems [33–39]. In addition, no statistical between group difference were detected in the long-term effects (demonstrated in SF-36) when we compared results of subjects with or without personal or family history of psychiatric disorder, see results.

The age- and gender matched control groups are large and ensure a valid comparison of the mefloquine group to the general Danish population. However, the control group does not represent a population that has traveled to tropical regions simultaneously with the study group. One can certainly view this as a limitation of the study. Traveling to tropical areas can give rise to cultural shock which can in itself result in a number of stress symptoms [40]. There is thus a risk of falsely attributing symptoms to mefloquine that could be due to the stress of traveling in itself. The recommendations in Denmark were already during the study period to start mefloquine prophylaxis three weeks prior to traveling. This would imply that most of the study subjects started experiencing symptoms before traveling since 77% had their symptoms debut within the first three weeks of treatment. Also, the hypothesis of neuropsychiatric events during use of mefloquine being partly explained by the psychological stress of traveling was not supported in a study conducted during

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the 3-week prophylactic period that precedes traveling [12].

5. Conclusions

Although it is not concluded that mefloquine results in more neuropsychiatric adverse events than other antimalarials, this study does give some support to the possible development of long-term mental health problems after mefloquine associated adverse events. It also gives a comprehensive clinically oriented picture of the spectrum of possible psychiatric problems in the acute phase. Future research should eliminate other explanations for the observed side effects, clarify possible interactions with other vulnerability factors, and explore possible methods to deal with adverse effects of medication.

Q2 Conflict of interest

None of the authors declared any conflicts of interests. The study did not receive support from the manufacture of mefloquine (Hoffman-La Roche, Basel, Schwitzerland). The initial statistical analysis was performed at Statens Serum Insitute and completed at Psychiatric Center North Sealand, Psychiatric Research Unit, Denmark.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tmaid.2014.10.021.

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Supplementary information

Acute and Long-term Psychiatric Side Effects of Mefloquine: A Follow-up on Danish Adverse Event Reports

Åsa Ringqvist[1,2], Per Bech[3,4], Birte Glenthøj[5,4], Eskild Petersen[6]

1 Department of Health Sciences, Lund University, Lund, Sweden

2 Department of Rehabilitation Medicine, Skane University Hospital, Lund, Sweden

3 Psychiatric Center North Sealand, Psychiatric Research Unit, Hillerød, Denmark

4 Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

5 Center for Neuropsychiatric Schizophrenia Research & Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Copenhagen University Hospital, Psychiatric Center Glostrup, Denmark

6 Department of Infectious Diseases, Aarhus University Hospital Skejby, Aarhus, Denmark

Corresponding author:

Åsa Ringqvist, MD, PhD

Department of Rehabilitation Medicine,

Lasarettsgatan 13

Skane University Hospital, Lund

221 85 Lund, Sweden

Phone: +46 46 171635/+46 70 4415889

Fax: +46 46 134837

E-mail: asa.ringqvist@med.lu.se

Methods

Symptoms Checklist-90-Revised (*SCL-90-R)*

The capability for SCL-90-R to detect clinical cases and to have acceptable validity for the diagnostic groups anxiety and depression has been shown in a primary care setting [1, 2]. Additionally, in a large patient group (n=1202) with personality disorders, the validity of the six subscales i.e. somatization (somatization and panic disorder), Obsessive-compulsive (Obsessive-compulsive disorder - OCD), interpersonal sensitivity (social phobia), depression (depression and dysthymia), anxiety (generalized anxiety), and phobic anxiety (agoraphobia) was confirmed by the finding of significant relationships with the associated DSM (Diagnostic and Statistical Manual of Mental disorder) disorder (except for the depression subscale with respect to dysthymia)[2].

Present State Examination (PSE)

PSE are a set of questions created by WHO with the aim of diagnosing mental illness. Questions from the PSE were used to ask about perceived cognitive function, disturbance of perception, hallucinations, and delusional mood / delusions.

Pilot

The questionnaire was sent to three persons outside the study group known to the investigators that had experienced side effects to mefloquine. After a structured interview, some final adjustments to clarify questions were made.

Telephone interviews

Nineteen subjects indicated delusional or hallucinative experiences in the questionnaire. Structured telephone interviews (using PSE) were carried out with 13 subjects. One subject clarified her symptoms by mail and one subject could not be reached by telephone. The experience of the latter subject was therefore rated as indicated in the questionnaire. The remaining four subjects were considered to have a less severe symptoms profile (see results) and had explained their symptoms clearly in the questionnaire.

Results

Hypomanic/manic states

Details of 4 patients with hypomanic/manic states

One subject, reporting hypomanic symptoms, was admitted under the diagnosis “observation for suspected mental and behavioral disorders”. Another subject reported manic symptoms and was post mefloquine admitted under the diagnosis “organic anxiety disorder” and “bipolar affective disorder” (This subject reported that she years prior to the adverse event had been treated for depression and also a brief psychotic state in response to the combined intake of alcohol and sedatives.). A third subject with no previous personal- or familial history of psychiatric disorders, reported hypomanic symptoms, but was not admitted to a psychiatric in-patient facility. Two subjects evaluated that their symptoms had lasted from 1-3 months and one subject indicated experiencing symptoms continuously. One subject was not considered a hypomanic/manic case since he, at the time, was admitted under the diagnosis acute and transient psychotic disorder unspecified and persistent delusional disorder unspecified.

Psychotic states

Only one of the subjects of the subjects describing a possible psychotic state had previously been admitted to any Danish psychiatric in-patient care prior to the adverse event e.i. one of the subjects who experienced delusional mood and delusions of reference with possible persecutory associations had 20 years previously been admitted to a psychiatric in-patient facility with the diagnosis hysterical neurosis.

Nightmares and cognitive problems

Recurring nightmares in response to mefloquine intake were reported by 59% of the study subjects, and 59% of the subjects stated cognitive problems in the questionnaire (memory, attentiveness, finding words, writing- and calculation abilities, and co-ordination), diminished attentiveness received the highest score i.e. 53%.

Hospitalizations

Nineteen study subjects (26%) reported having been hospitalized in association with the mefloquine triggered event. Fourteen (19%) reported hospitalization primarily due to side effects of mefloquine. Cross-checking with the Danish Psychiatric nation-wide case register showed that ten (14%) had been admitted to psychiatric in-hospital ward units post mefloquine intake. Thus, four (5.4%) of the study population were hospitalized due to physical side effects and ten subjects (14%) due to psychiatric symptoms. Out of the 10 individuals receiving in-hospital psychiatric care, eight (10%) had reported perceptual disturbances/hallucinations and/or delusional experiences/delusional mood in response to mefloquine intake. Thus, psychotic states were the most common reason to receive in-hospital psychiatric care.

Psychopharmacological treatments

Twenty-two subjects (32%) had been prescribed psychopharmacological medication. Antidepressive drugs (serotonin reuptake inhibitors, Tricyclic antidepressants) (one person in combination with a antipsychotic compound) were prescribed to 15 % of the mefloquine group and 7% were prescribed antipsychotic drugs (one person in combination with a antidepressant drug). Sedatives were prescribed to 12 % of the subjects as the single psychopharmacologic treatment and also used in some of the above cases in addition to antidepressive- or antipsychotic drugs. 22% of the study population received psychotherapeutic treatment and 4 % sought help from alternative medicine.

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