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

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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.

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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 indicated 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].