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Neuropsychiatric manifestations after mefloquine therapy for *Plasmodium falciparum* malaria: comparing a retrospective and a prospective study

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Summary Mefloquine has been increasingly used for treatment of chloroquine-resistant malaria since its introduction in the late 1970s. In 1987 the first case of toxic encephalopathy was published, and in 1989 the WHO initiated reporting and investigation of neuropsychiatric adverse reactions of mefloquine. Neuropsychiatric adverse drug reactions are now well documented. We compared an open prospective 3 year study including all patients with *P. falciparum* treated with mefloquine with an earlier published, retrospective study on a comparable population from our department covering the period up to 1989.

In the retrospective study neuropsychiatric adverse effects were not specifically asked for, while in the prospective study possible adverse reactions were registered daily according to a specified questionnaire. No case of neuropsychiatric adverse reaction was registered in the retrospective study. In the prospective study, 28% had one or more neuropsychiatric adverse reactions, although severity was mostly mild to moderate. Other adverse reactions occurred in 96% in the retrospective study compared to 81% in the prospective study. In conclusion: one often finds only what one looks for, e.g adverse events may be overlooked for a decade, if relatively uncommon. This report also shows that retro- and prospective studies may give very different results.

keywords malaria, mefloquine, neuropsychiatric, adverse reactions, retrospective and prospective studies

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Introduction

Mefloquine (Lariam), a 4-quinoline methanol derivative, chemically related to quinine, has been increasingly used for treatment of chloroquine resistant malaria since its introduction in the late 1970s. In the first decade of widespread mefloquine usage published adverse drug reactions to mefloquine were mainly gastrointestinal – nausea, vomiting and diarrhoea (Magnussen & Bygbjerg 1990; Palmer *et al*. 1993).

A report on possible mefloquine-induced toxic encephalopathy in 1987 (Bernard *et al*. 1987) was followed by 13 additional cases in 1989, which prompted the WHO in collaboration with the manufacturer (F. Hoffmann-La Roche) to investigate the neuropsychiatric adverse events related to mefloquine (WHO 1991). The investigation was based on adverse events case report forms sent either to the pharmaceutical company or to WHO; an estimated rate of major psychiatric events of 4.2/1000 and seizures of 2.4/1000 was reported (WHO 1991). Interim guidelines were published and intensive surveillance was initiated in 1989 (WHO 1989). Neuropsychiatric adverse reactions of mefloquine are now well documented (Phillips-Howard & ter Kuile 1995). The incidence during treatment ranges from 1/159 to 1/1217 in different settings (Weinke *et al*. 1991; Sowunmi *et al*. 1993; ter Kuile 1994; Phillips Howard *et al*. 1995).

The delay in recognizing the potentially severe adverse drug reactions to this commonly used antimalarial drug prompted us to review the literature on mefloquine treatment before and after the WHO warnings issued in 1989. We initiated a prospective 3 year study to compare it with an earlier published retrospective study from our own department covering the period up to 1989 (Magnussen & Bygbjerg 1990).

Materials and methods

Literature review

The review of the literature on neuropsychiatric adverse drug reactions after mefloquine treatment encompassed clinical trials and case histories available on MEDLINE, and reported to WHO and the producer (WHO 1991; F. Hoffmann-La Roche 1993). Reference lists from published papers were also reviewed.

Copenhagen retrospective study

At our department mefloquine was introduced in 1982 for therapy of patients with *P. falciparum* malaria suspected resistant to chloroquine and sulphadoxine-pyrimethamine; in 1987, it became standard therapy for uncomplicated falciparum malaria. All patients with microscopically verified *P.falciparum* malaria admitted in the period 1982–88 and treated with mefloquine were included in the retrospective survey (Magnussen & Bygbjerg 1990).The patients, 81 in total, were seen daily during admission and 1 and 4 weeks after initiation of therapy.

Patients were routinely asked about symptoms during treatment, including nausea and vomiting. During the review of the patients' files, any possible adverse reaction as well as the clearance of parasites and fever was noted on a data sheet.

Copenhagen prospective study

Consecutive patients with microscopically verified *P.falciparum* malaria were included in the study from 1990 to 1993. Possible adverse reactions were registered daily according to a questionnaire which listed nausea, vomiting, diarrhoea, dizziness, tinnitus, headache, sleeplessness, irritability, restlessness, anxiety, nightmares, depression, mania, hallucinations, weakness, paraesthesia, tremor, convulsions and coma. A serious adverse reaction was defined as one which was fatal, life-threatening, disabling and/or resulting in or prolonging a patient's stay in hospital.

Patients were seen daily during the hospital stay and 1 and 4 weeks after initiation of therapy. Sixty-one patients were followed, of whom 54 received mefloquine only. Severe and complicated malaria cases (7 patients) treated with intravenous quinine were excluded from the analysis.

Results

Literature review

Excluding cases of nondisabling or mild adverse reactions according to the authors (e.g. headache, dizziness, sleeplessness or abnormal dreams), we found 44 published cases of moderate to serious neuropsychiatric adverse events after mefloquine treatment in 18 papers, of which only three (Ekue *et al*. 1983; Harinasuta *et al*. 1983; Bernard *et al*. 1987) were published before 1989, the remainder after 1989 (Bernard *et al*. 1989; Patchen *et al*. 1989; Rouviex *et al*. 1989; Stuiver *et al*. 1989; Luxemburger *et al*. 1991; Weinke *et al*. 1991; Caillon *et al*. 1992; De Gennes *et al*. 1992; Marsepoil *et al*. 1993; Sowunmi *et al*. 1993; Hennequin *et al*. 1994; Rønn and Bygbjerg 1994; Sowunmi 1994; Speich & Haller 1994; Sowunmi *et al*. 1995).

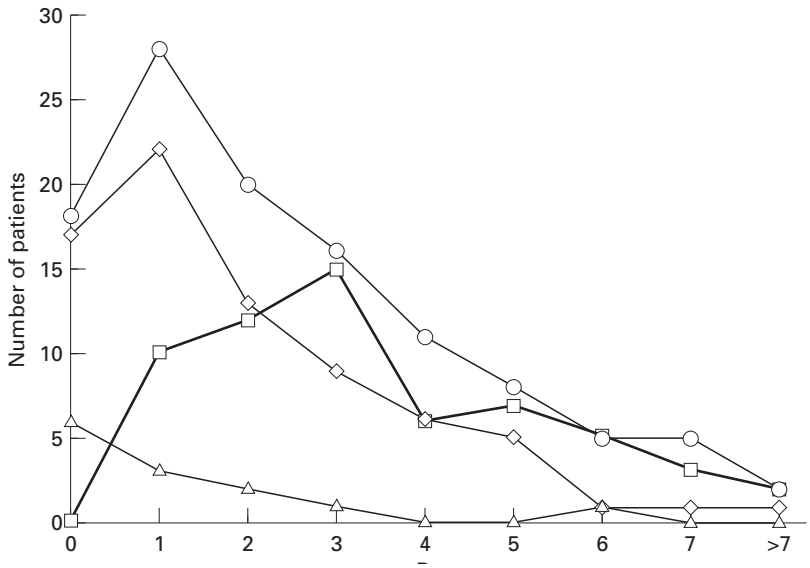

Figure 1 The most prevalent complaints of patients with *P. falciparum* malaria relative to mefloquine intake. ○ dizziness; ◇ nausea; △ vomiting; □ neuropsychiatric events.

The majority of the reports were single case reports or open trials not specifically designed to detect adverse events. In most trials the method of collection of adverse events was not described. Excluding trials with mefloquine given together with other antimalarials we found only five studies which were randomized and blinded. All studies were conducted before 1989 (Ekue *et al*. 1983; Harinasuta *et al*. 1983, 1985; Ahn *et al*. 1990; Thimasarn *et al*. 1990). A total of 2 cases of neurological or neuropsychiatric adverse drug reactions were reported out of 567 treated patients (Ekue *et al*. 1983; Harinasuta *et al*. 1983), e.g. 0.4%. If milder cases are also included, at least twice as many cases were reported, since in the WHO report (1991) 46 of 98 cases were considered serious.

Copenhagen retrospective study

In this study, all drug reactions were relatively mild. Most patients complained of nausea after taking the tablets (93%); in 10 of 81 patients (12%), vomiting appeared within one hour after medication, necessitating an extra dose of mefloquine. Seventy-seven of the patients were seen one week after discharge and 46 one month after discharge. No neurological or neuropsychiatric adverse drug reactions were noted (Magnussen & Bygbjerg 1990).

Copenhagen prospective study

Sixty-one patients with *P.falciparum* malaria admitted 1990–93 were treated with mefloquine. Seven of these patients were excluded from analysis since they were also treated with intravenous quinine and had severe and complicated malaria. The mean duration of hospital stay was 4 days; 48 patients were seen as outpatients one week after start of treatment and 44 four weeks after start of treatment.

The most prevalent complaints (Figure 1) are shown relative to time of mefloquine intake. Twenty-five patients (46%) had nausea and 9 (17%) vomited. It should be noted that we classified dizziness as a non-neurological adverse reaction. Fifteen patients (28%) had one or more neuropsychiatric adverse reactions, albeit mostly mild to moderate, including; hallucinations, nightmares, depression, anxiety, sleeplessness and mania (Table 1). The majority of reactions were transient and resolved spontaneously, except in two patients: one female patient suffered from serious behavioural disorders such as hallucinations, paranoia and

Table 1 Adverse drug reactions after mefloquine treatment

	1982–1988 Copenhagen retrospective study (n = 81)		1990–1993 Copenhagen prospective study (n = 54)	
	n	%	*n*	%
Non-neuropsychiatric adverse events				
nausea	78	96	25	46
vomiting	10	12	9	17
dizziness	0	0	29	54
Percentage of patients with one or more non-psychiatric adverse reaction	78	96	44	81
Neuropsychiatric adverse events				
Restlessness	0	0	5	9
Sleeplessness	0	0	4	7
Nightmares	0	0	2	4
Hallucinations	0	0	1	2
Mania	0	0	1	2
Anxiety	0	0	1	2
Depression	0	0	1	2
Tremor	0	0	5	9
Paraesthesia	0	0	3	6
Percentage of patients with one or more neuropsychiatric adverse reaction		0	15	28
Mild to moderate adverse reactions	0	0	13	24
Severe adverse reactions	0	0	2	4

mania, another patient had severe nightmares and depression, requiring extended hospitalization for both. These patients had no personal or family history of neuropsychiatric disorder, alcohol abuse or drug history, nor was there any evidence of concomitant infections.

Of the 7 patients who were excluded because of comedication with quinine, one female patient developed acute brain syndrome 2 weeks after medication. She was rehospitalized and developed coma and generalized convulsions; the symptoms resolved slowly over the next 4 weeks (Rønn & Bygbjerg 1994).

Comparing Copenhagen retrospective and prospective studies

The retro- and prospective studies were comparable with regard to mean age (27 *vs*. 34 years) and sex (68% *vs*. 70% males). The dose of mefloquine was the same, a total of 1.5 g = 6 tablets for patients weighing at least 60 kg, 1.25 g for others. However, all patients in the prospective study got mefloquine in divided doses: 3 tablets followed by 2 Tablets 6–8 h later and one after another 8 h if the patient weighed more than 60 kg, whereas about half of the patients in the retrospective survey received a single dose of 6 (or 5) tablets.

Parasitological cure, e.g. no trophozoites in the blood, was seen within 3.6 days in the retrospective and within 4 days in the prospective study. The temperature returned to normal after a mean of 2.7 days in the retrospective study and 2.4 days in the prospective study.

The patients were also comparable regarding parasitaemia, duration and severity of the disease. In both studies, most patients were seen by only two doctors, one of whom participated in both studies. In spite of this, a striking difference was observed between the two studies: no case of neuropsychiatric adverse reaction was registered in the retrospective study, while 15/54 = 28% had such adverse reactions in the prospective study. Other adverse reactions occurred in 96% (78/81) in the retrospective study compared to 81% (44/54) in the prospective study.

Discussion

No neuropsychiatric adverse drug reactions were noted in the retrospective survey while 28%, mainly mild, were reported in the prospective study. The retrospective study disclosed many gastrointestinal adverse effects, probably because the drug was recently introduced and the authors were aware of and expected nausea and vomiting. During the prospective study, nausea and vomiting were considered trivial and well-known adverse reactions, while the neuropsychiatric adverse reactions were in focus following the warnings by WHO.

The usage of single doses in some patients may have contributed to the higher incidence of nausea in the retrospective survey. It should be noted that for symptoms such as dizziness, headache, nausea and diarrhoea it is difficult to distinguish between symptoms of malaria and adverse reactions caused by mefloquine. In this study neuropsychiatric adverse reactions peaked on day 3 (Figure 1), when most of the patients had cleared parasitaemia and their temperature had returned to normal. It is less likely that these reactions were caused by the disease, which was mild to moderate and generally resolved within 2–3 days.

Other potential predisposing factors, including coinfection and immune mechanisms, may contribute to neuropsychiatric disorders (Silva *et al*. 1992; Rønn & Bygbjerg 1994; F. Hoffmann La Roche 1993); thus mefloquine is not the only risk factor for malaria-related neurological syndrome, but is considered a strong one as described by Mai *et al*. (1996). A prospective randomized study of postmalaria neurological syndrome (PMNS) showed that PMNS was associated with the use of mefloquine. 4.4% of patients with severe malaria who received mefloquine developed PMNS compared with 0.5% of those receiving quinine (Mai *et al*. 1996).

In our retrospective study, mild neuropsychiatric adverse effects were probably overlooked since they were not specifically asked for. Severe neuropsychiatric adverse effects are rare and may be overlooked, even up to 10 years, as indicated by the review of the literature on mefloquine trials and case reports of adverse events.

Reliable recording of adverse events is not easy. A carefully designed double blind randomized trial is obviously the gold standard for clinical research which may eliminate many of the problems. Spontaneous reports of adverse events have severe limitations. They are probably most reliable for serious events. A geographical bias was also apparent in our review of the literature. Except for 5 papers (Ekue *et al*. 1983; Harinasuta *et al*. 1983; Sowunmi 1994; Sowunmi *et al*. 1993, 1995), all case histories referred to patients treated in the industrialized world, mainly Europe.

Some studies have shown that more women than men report neurological or psychiatric adverse events (WHO 1991; Phillips-Howard & ter Kuile 1995; ter Kuile *et al*. 1995; Schlagenhauf *et al*. 1996). Therefore, gender should also be taken into consideration. Accordingly, dizziness was reported by 14/38 (37%) men and 12/16 (75%) women in our prospective study. In most clinical trials, the majority of the patients are men; some studies even exclude women, because of the fear of treating pregnant women.

While different studies report varying incidences of neuropsychiatric adverse drug reactions during mefloquine treatment, the increased frequency of neuropsychiatric side-effects during prophylactic mefloquine use has

prompted extensive debate. Weinke *et al*. (1991) estimated the incidence of neuropsychiatric adverse reactions during prophylaxis as 1:1300; by comparison a recent retrospective study found that disabling neuropsychiatric side-effects occurred in 1:140 of travellers taking mefloquine for prophylaxis (Barrett *et al*. 1996). Another recent study showed that 7.9% (33:420) of travellers taking mefloquine reported minor neuropsychiatric adverse effects, but no serious adverse effects (Schlagenhauf *et al*. 1996). In 1996 the Department of Drug Safety of F. Hoffmann-La Roche reported a total of 3827 adverse events, 87 for curative treatment. 55% of the adverse events were of neuropsychiatric nature (Dankwa & Martin 1997).

Conclusion and recommendations

One often finds only what one looks for. Our report underlines that retro- and prospective studies may give very different results even though both studies were carried out under almost the same conditions. One of our main aims is to stress on how difficult it is to get an 'exact' and objective estimate of the incidence of adverse drug reactions (here neuropsychiatric). We are not exactly proud of disclosing that we may have overlooked more than 20% of potentially severe side-effects for 10 years of mefloquine use, but the current discussions on the incidence and severity of mefloquine related side-effects, including the users charges on the medical profession, in our view call for more openness.

In the UK, where the safety of mefloquine has received considerable media attention, the frequency of reporting adverse events increased more than 100% from 1995 to 1996. 66% of cases reported came from the UK (Dankwa & Martin 1997). Severe adverse events may be overlooked for a decade if relatively uncommon. Therefore every single serious possible adverse drug events should be communicated.

WHO recommends to take precautions with prescription of mefloquine to patients with a history of seizures or pre-existing psychiatric disorder (WHO 1991). While reversible neuropsychiatric reactions after use of mefloquine to treat a potentially fatal disease may be regarded as relatively 'acceptable' in controlled hospital settings, recent reports of serious disabling neuropsychiatric adverse effects during prophylaxis (Barrett *et al*. 1996) are worrying.

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