



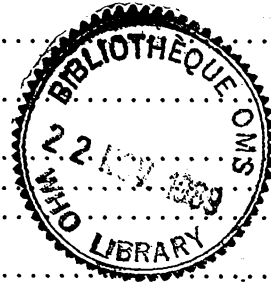
*Chemicals - adv. effects
Central nervous system - drug eff
antimalarials - adv. eff.*

CENTRAL NERVOUS SYSTEM REACTIONS RELATED
TO THE ANTIMALARIAL DRUG, MEFLOROQUINE¹

26920

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¹ Report of an informal consultation held in Geneva on 17 July 1989 and organized by Research and Technical Intelligence, Malaria Action Programme and the Scientific Working Group on the Chemotherapy of Malaria, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. For list of participants, please see Annex 1.

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1. INTRODUCTION

Chloroquine-resistant Plasmodium falciparum poses a problem for treatment and prophylaxis in many countries of South East Asia, Africa, South America and Oceania. Widespread resistance of P.falciparum to chloroquine has necessitated the development of new drugs. One such drug, mefloquine hydrochloride, a quinoline methanol derivative chemically related to quinine was developed by the Walter Reed Army Institute of Research, in collaboration with the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the pharmaceutical company, F.Hoffman-La Roche. Preclinical evaluation of its antimalarial activity, its pharmacology and toxicity did not show any mutagenic, carcinogenic or other serious toxicity, even at relatively high doses. When administered to rats over a period of two years, mefloquine was non toxic at daily doses of 5mg/kg but toxic effects were evident at higher doses of 20-50mg/kg administered daily. No toxic effects were evident when administered to dogs for a one year period in daily doses of between 5-150mg/kg (UNDP/World Bank/WHO, 1983). Clinical and field trials including, dose finding studies, have shown mefloquine to be an effective and well tolerated drug for therapy (De Souza, 1983; Harinasuta et al, 1983; Kofi-Ekue et al, 1983) and prophylaxis (Pearlman et al, 1980). Pharmacokinetic studies have shown that mefloquine reaches peak blood concentrations (0.9-1.0ug/ml) 2-12 hours after drug administration, but that it is highly plasma-bound and is slowly excreted. It thus has a long but variable elimination half life ranging from 13-26 days (Desjardins et al, 1979; Schwartz et al, 1983).

Mefloquine has been registered in a number of countries for prophylactic and therapeutic use, including Austria, France, Holland, Sweden, Switzerland, West Germany and the USA. It has also been registered in Thailand and deployed in the malaria control programme as a fixed combination with sulfadoxine/pyrimethamine. There have recently been several case reports documenting serious neurological and psychiatric reactions apparently related to mefloquine use for malaria therapy (Bernard et al, 1987; Rouveix et al, 1989; Stuver et al, 1989) and for prophylaxis (information provided by F.Hoffman-La Roche, Basle and spontaneous reports to WHO). The risks of such reactions have not been fully investigated.

The WHO Scientific Group on the Chemotherapy of Malaria reviewed in June 1989 the initial reports of these neurological and psychiatric reactions. The members of this Group recommended that the Malaria Action Programme, WHO, should examine all available reports in more detail and develop a surveillance system to obtain further information of these adverse events associated with mefloquine, as well as those related to the use of other antimalarial drugs.

This report reviews the data on neurological and psychiatric reactions attributed to mefloquine which were available to WHO and Hoffmann-La Roche in July 1989. These data originate from controlled clinical trials conducted by WHO and TDR, surveys of travellers and spontaneous reports to both Hoffmann-La Roche and WHO. The amount of information on each report of a serious reaction is variable and the follow-up of the cases limited. It is, therefore, often impossible to prove conclusively that the reported event is related to the use of the drug. It is also impossible at present to determine the frequencies of these events because of the limitations of spontaneous reporting and the difficulties of obtaining valid denominators, i.e. the number of prophylactic and therapeutic doses used. Thus, this report also highlights the need to investigate systematically the types and frequency of mefloquine-associated reactions.

2. TYPE AND FREQUENCY OF NEUROLOGICAL AND PSYCHIATRIC REACTIONS

Information on the type and frequency of neurological and psychiatric reactions following mefloquine use was derived from clinical trials data, spontaneous reports from volunteers or patients treated for malaria and surveys of travellers. Cases were divided into those associated with either the prophylactic or therapeutic use of mefloquine. All reactions were included which could broadly be defined as neurological or psychiatric. These include reactions ranging from fatigue and asthenia to seizures, and acute psychosis (Table 1). The gradation of mild through to severe was based on the degree of impairment of autonomous functioning and performance on the part of the person affected.

2.1 Prophylaxis

2.1.1 Drug trials

A total of 1587 persons received mefloquine in prophylactic trials conducted in Thailand in 1977 and 1983-4 and in Malawi in 1987-9. No severe neurological or psychiatric reactions were reported in the Thailand trials, which included 110 adult males taking 250mg of mefloquine weekly for one year (L. Pang, personal communication) or observed in the Malawi study. The frequency of other side effects in the Malawi study was lower in the group receiving mefloquine than that receiving chloroquine. Dizziness occurred with equal frequency in both groups (C.C. Campbell, personal communication).

2.1.2 Traveller surveys

A total of 7789 travellers using mefloquine for prophylaxis has been monitored during travel surveys conducted in Europe.

One such study included 4248 Swiss and other European users (R. Steffen, personal communication). Dizziness was reported by 5% of these users of mefloquine. A similar proportion (4.5%) of chloroquine users reported the same reactions. Depression, headache and sleeping disorders were also reported as reactions following the use of both mefloquine and chloroquine. These disorders are, however, not unusual in travellers not taking medication. Two travellers using mefloquine prophylaxis sought medical attention for neurological and psychiatric reactions. One had depression lasting nine months, and the other was an alcoholic who developed a phobia. No fatalities were reported and none of the reactions to mefloquine required hospitalization. There were no reports of anxiety, confusion, seizures or coma following either mefloquine or chloroquine use.

In a similar study conducted in Berlin, Federal Republic of Germany, 2.2% of 1745 persons taking mefloquine prophylaxis reported adverse effects (T. Weinke, personal communication). These conditions were mild and included drowsiness or dizziness, visual disturbances, disorders of balance, and sleep disorders. The frequency of these reported adverse effects was similar in both mefloquine and chloroquine users, but data were unavailable to allow a comparison of the relative frequency of neurological reactions. In a separate study of Germans conducted in Hamburg 9% and 20% of 175 travellers taking mefloquine or the triple combination of mefloquine/sulfadoxine/pyrimethamine respectively for prophylaxis experienced mild reactions, none of which were neurological or psychiatric. All resolved spontaneously within seven days following discontinuation of prophylaxis. No severe adverse effects were reported (K. Volkner, personal communication).

A survey of travellers departing from Nairobi for Europe or North America showed that 177 respondents (predominantly French) used mefloquine prophylaxis (Lobel et al, 1989). No neurological or psychiatric reactions were reported in this group and other adverse effects were reported at a similar frequency to that observed in other travellers taking chloroquine. No one with adverse effects required medical attention. 23% of 1444 travellers experienced reactions following mefloquine use in another survey of French travellers (M. Armengaud, personal communication). Four percent of these travellers experienced serious reactions, and 1.6% neurological or psychiatric adverse effects. Detailed information on the severity and management of these cases was unavailable.

2.1.3 Spontaneous reports to WHO

Severe neurological and psychiatric reactions were reported from Thailand in four French travellers, 3 males and one female, taking 250 mg mefloquine per week for prophylaxis. Three of the travellers lost consciousness and had convulsions 1 or 3 days after the second or third tablet of mefloquine. The fourth became depressive, had hallucinations and became suicidal three days after the third tablet of mefloquine (Tranakchit Harinasuta and Danai Bunnag - personal communication).

2.2. Therapy

2.2.1. Clinical and field trials conducted by WHO/TDR

Mefloquine, as a monosubstance, has been administered alone at treatment doses of 500-1250 mg base to 735 adult males and females in controlled clinical and field trials conducted from 1977-1989 under the auspices of either TDR or MAP in Brazil, Thailand and Zambia. These included 82 pregnant women suffering from acute falciparum malaria. It has also been used in studies by the Centers for Disease Control, USA as a single dose of 750 mg to sterilize infections in 689 pregnant women in Malawi during 1987-1989. Dizziness and gastrointestinal adverse effects were the most commonly reported reactions, although it is often not clear how many of these events can be attributed to malaria. Dizziness and gastrointestinal adverse effects were also observed at a more or less equal frequency with chloroquine and sulfadoxine/pyrimethamine when these drugs were used in comparative double-blind trials with mefloquine. A total of 9 neurological and psychiatric events, following mefloquine treatment were reported from the above studies (Table 2).

No adverse effects classified as "severe" were observed in the Malawi study conducted in Malawi or in clinical trials conducted in Brazil where 55 patients received 1000 mg mefloquine as a single dose.

In a recent trial in the U.S., all seven healthy adult males who received a single dose of 15mg/kg mefloquine base showed neurological reactions, including severe dizziness, light-headedness, vertigo and difficulty in concentration (C.C. Campbell, personal communication).

Mefloquine has also been used as a triple combination with sulfadoxine and pyrimethamine in clinical and field trials conducted by TDR and WHO (Kofi-Ekue *et al*, 1985, 1987; de Souza *et al*, 1987; Harinasuta *et al*, 1987). 500 volunteer patients received the drug in doses ranging from 1-3 tablets (each tablet containing 250 mg mefloquine base, 500 mg sulfadoxine and 25 mg pyrimethamine). A total of five cases of severe neurological or psychiatric reactions were reported, of which four were from clinical trials in Zambia and one from Thailand (Table 3). No severe reactions were reported from Brazil where 160 patients received the same formulation.

Neurological reactions have also been reported from trials in which primaquine has been administered with single treatment doses of 750-1000 mg mefloquine base. In a Phase I tolerance and pharmacokinetic study, all seven volunteers receiving a single dose of 1000 mg mefloquine and 30 mg primaquine complained of light-headedness, euphoria or dysphoria, slowed reactions and a pronounced inability to conduct normal, particularly mental, activity. Three of the seven required bed-rest. These adverse effects, which appeared within 4-12 hours after receiving mefloquine and the first daily dose of primaquine, abated within 4 days. Such severe reactions were not observed in seven other volunteers receiving 1000 mg mefloquine alone (H. Frischer, personal communication). This trial was not completely controlled and the high incidence of subjective adverse effects could result from "association and suggestion" since the subjects were studied simultaneously.

287 patients received 750 or 1000 mg mefloquine together with a single 45 mg dose of primaquine either on day 0 or 3 in an outpatient study in Thailand. Mental confusion was reported in two patients given 1000 mg mefloquine and 45 mg mefloquine on day 0. These symptoms developed on day 0 in one case and three days after drug treatment in the other. Another patient receiving the same drug regimen developed visual distortion lasting for 24 hours on the day following drug administration. Mental confusion was also reported in four other patients receiving 750 mg mefloquine followed by 45 mg primaquine on day 3. These symptoms arose between 1 and 3 days following mefloquine treatment and all patients recovered within 2-3 days (Surin Pinichpongse, personal communication). In contrast, no severe reactions were observed in a similar trial conducted in a hospital in Thailand in which 34 patients received 750 mg mefloquine and 45 mg primaquine as a single dose on day 0 (Tranakchit Harinasuta, personal communication).

2.2.2. Other experience with treatment doses

47% of all travellers in a Swiss survey of 135 travellers taking a treatment dose of 750mg mefloquine following their return from an endemic area experienced dizziness, which was often severe but more intense neurological or psychiatric symptoms were not reported. However, 14 severe side effects have been reported to WHO following the treatment of falciparum infections in France, Holland and Thailand with either mefloquine alone (11 cases) or a combination of mefloquine/sulfadoxine/pyrimethamine (3 cases) (Table 4). The symptoms included paresthesia, megalomania, amnesia, seizures, hallucinations and psychotic behaviour. 7 of these cases had received 1500 mg mefloquine, 2 had received 1250 mg mefloquine, one had received 1000mg mefloquine and two had received three tablets of mefloquine/sulfadoxine/pyrimethamine. The remaining case was a girl of 5 years who had received mefloquine at a dose of 20mg/kg. 4 of the above cases, including the most severe, had either taken quinine just before or after mefloquine treatment and another had also been treated with tablets and one injection of unknown origin prior to the diagnosis and treatment with the mefloquine triple combination.

3. CHARACTERISTICS OF CASES WITH NEUROLOGICAL AND PSYCHIATRIC REACTIONS

Both producers of mefloquine, F. Hoffman-La Roche, Basle and Mepha A.G., Dornach, market the drug as a tablet formulation of 250 mg mefloquine hydrochloride. Spontaneous reports of serious reactions suspected to be due to mefloquine have been received by F. Hoffman-La Roche, but not by Mepha A.G. (This latter company has only a relatively small proportion of the mefloquine market).

Cases of neurological and psychiatric reactions associated with mefloquine, reported to Hoffman-La Roche, were analyzed in an attempt to assess their epidemiological characteristics. Additional cases reported to WHO, but not yet to the pharmaceutical company, were also included in the analyses if the case reports forms provided adequate information. The temporal relationship with the use of mefloquine was assessed, and some of the possible causal associations with risk factors were explored. Cases were again subdivided according to use, i.e. prophylactic or therapeutic. The frequency of reactions was not estimated because of the many biases with the spontaneous reporting of adverse events associated with a newly marketed drug, and since it was impossible to obtain valid denominators of the number of prophylactic or therapeutic doses used.

3.1. Spontaneous reports to the pharmaceutical company

A total of 274 case reports of adverse effects suspected to be due to mefloquine has been received by F.Hoffmann-La Roche as of June 1989.

3.1.1 Mild events

The number of occurrences of mild events (more than one may have been reported per case) included:

- vertigo	29	occurrences
- headache and head		
- pressure	10	" "
- dizziness	6	" "
- ataxia	1	" "
- Dysequilibrium	3	" "

3.1.2. Psychiatric disorders

There were 40 cases reported to Hoffman-La Roche with one or more adverse events in the system organ class 0500 (psychiatric disorders), 27 of these reports were considered to have definite psychiatric characteristics. Of these, 14 persons had taken mefloquine for prophylaxis, 11 patients had received mefloquine for malaria treatment and in two the indication for mefloquine use was not known. The remaining 13 of the 40 reports were considered by the company not to include adverse effects clearly defined as psychiatric. These included such symptoms as trembling, fatigue, abnormal hunger, and disturbed sleep. They have not, therefore, been included in further analyses. There was an equal number of males and females (mean age 36 years; range 6-76 years) reported with psychiatric disorders. There were no fatalities in any of the above 40 cases.

3.1.3. Neurological system disorders

27 cases reported to Hoffman-La Roche had one or more adverse events in the system order class 0410 (central and peripheral nervous system disorders). 15 of these presented with seizures with or without postictal coma, confusion or memory disturbance (2 cases with "tetany" were included); 6 had taken mefloquine for prophylaxis and 9 for therapy of malaria. Nine cases were males, and six females; the mean age of the group was 30 years (range 4 to 55 years). No fatal outcome was reported. The remaining 12 of the 27 reports in this category included cases with mild adverse effects, such as, vertigo, headache and dizziness.

3.2. Analyses of epidemiological characteristics

The 27 cases with definite psychiatric disorders, and the 15 cases with seizures reported to Hoffman-La Roche were pooled together with 20 additional cases reported to MAP/WHO from Thailand, Zambia and the Netherlands. The latter included 17 cases with psychiatric disorders and 3 with seizures.

3.2.1. Temporal association between drug intake and onset of reactions

Therapy is commonly administered within a 24 hour period, thus, for patients with reactions following therapy the time interval was measured from the day of therapy to the day symptoms were first experienced. For persons on prophylaxis, the time interval measured was the number of weeks prophylaxis had been taken before symptoms first developed.

The onset of adverse effects following therapy occurred within four days in 21 of 26 cases with psychiatric reactions, and in 4 of 7 cases with seizures (Table 5). The longest interval between treatment and a psychiatric reaction attributed to mefloquine was 21 days. Both psychiatric reactions and seizures were reported after taking the first prophylactic dose of mefloquine. All attacks of seizures occurred within three weeks, whilst some psychiatric reactions were first experienced during the second month of prophylaxis.

3.2.2. Dose relationship

Correlation of the amount of mefloquine taken and the severity of serious adverse effects was difficult. Some relationship with dose, however, was apparent. For example, 5 out of the 16 psychiatric cases following mefloquine prophylaxis were psychotic. These only occurred after 3 to 5 weekly doses of 250 mg mefloquine. The psychiatric symptoms in the remaining travellers tended to be milder and were manifested sooner. In contrast, there appeared to be no obvious difference in the total dose of mefloquine received in psychotic events spontaneously reported during treatment with mefloquine. Symptoms associated with therapeutic doses of mefloquine were judged severe in 5 out of 11 case reports of psychiatric events, and mild in 6 of the 11 case reports. The total therapeutic dose of mefloquine given in the group with more severe manifestations was 1250mg/case as compared to an average of 1458mg/case for the other group reporting to milder symptoms. Seizures following therapy were not reported at doses below 1000mg.

3.2.3. Previous neurological or psychiatric histories

None of the 7 cases with seizures and 1 of 7 cases with psychiatric disorders, whose previous medical history was known, had previously experienced similar reactions prior to treatment with mefloquine (Table 6). Three of 10 cases experiencing seizures while on prophylaxis had a past history of this disorder, and 2 of 8 prophylactic users with psychiatric reactions were known to have a previous

psychiatric history (Table 6). It is not known what proportion of mefloquine users, who have not experienced any neurological or psychiatric reactions, have had a history of such disorders yet remained healthy while taking mefloquine.

3.2.4. Recent or concurrent use of other antimalarials

The use of other antimalarials was common among cases reported to have adverse effects associated with mefloquine therapy. 17 of the 40 cases reported with psychiatric events had used other antimalarial drugs, as had 6 of 7 cases with seizures (Table 7). A proportion of cases using mefloquine for prophylaxis had also taken other antimalarials; 4 of 9 with psychiatric events, and 4 of 10 with seizures. No data are currently available on the proportion of mefloquine users who have previously or concurrently used other antimalarial drugs.

4. REPORTS OF NEUROLOGICAL AND PSYCHIATRIC REACTIONS FOLLOWING USE OF OTHER ANTIMALARIAL DRUGS

Three cases of neurological and psychiatric reactions associated with the "comparison" drug were reported from double-blind trials of mefloquine treatment in Zambia. Two male patients received oral chloroquine, 600 mg followed 2-6 hours later by a further 300 mg and then 300 mg daily for 2 days. One patient had seizures and momentary loss of consciousness 16 hours after receiving the first dose of chloroquine. He recovered within one day. There was no neurological deficit and no history of epilepsy (Kofi-Ekue, et al, 1983). The second patient became restless, uncooperative and violent 8 days after receiving the first dose of chloroquine. He recovered following treatment with diazepam. The third patient complained of visual hallucinations 20 days after receiving 3 tablets of sulfadoxine/pyrimethamine. The patient was found to be tense, apprehensive and worried, but orientated in time and place. He had no previous history of such effects and denied use of drugs or alcohol. He recovered following treatment with diazepam. (Both unpublished reports - J.M. Kofi-Ekue, personal communication).

5. CONCLUSIONS

Certain tentative conclusions may be drawn from the above data. However, these may need to be revised in the future in the light of further information and follow-up of existing case reports.

5.1. Characteristics of risk

- (i) Neurological and psychiatric reactions have been reported following the therapeutic and prophylactic use of both mefloquine alone and mefloquine in fixed combination with sulfadoxine/pyrimethamine for both treatment and prophylaxis.
- (ii) The incidence of these adverse effects following the use of these formulations for treatment may be in the order of 1% based on reports from clinical and field trials.
- (iii) Such adverse effects have been reported following the administration of doses ranging from 500 mg-2000 mg mefloquine base alone or of two or three tablets of the triple combination of mefloquine/sulfadoxine/pyrimethamine (= 500 or 750 mg mefloquine base).

- (iv) A greater number of neurological and psychiatric reactions have been reported following the administration of treatment doses of 1000 mg and above of mefloquine, although the incidence is difficult to calculate due to small numbers of cases and the lack of valid denominators.
- (v) No serious neurological or psychiatric events have been reported in prophylactic drug trials of mefloquine.
- (vi) Limited evidence suggests that there may be a relationship between the severity of the adverse reactions and the accumulated prophylactic dose, but this requires further study.

5.1.2. Causal association with risk factors

- (i) The proportion of neurological and psychiatric adverse effects in males and females was similar, their ages ranging from the young (approximately 5 years) to the elderly (more than 70 years).
- (ii) The role of previous or concomitant use of other antimalarial drugs has yet to be established. Absence of a control group prevents any clear assessment of causal relationships.
- (iii) A previous history of neurological and psychiatric disorders was observed in several persons with reactions attributed to mefloquine prophylaxis. It is not clear whether these reactions became manifest as a result of the drug or were part of an ongoing illness.
- (iv) Other risk factors, not routinely documented, need to be explored, for example, concomitant illness, alcohol use and allergies.

5.2. Current guidelines for mefloquine use

The data available so far are not adequate to suggest changes in current guidelines for the use of mefloquine. However, they do suggest that it is advisable that mefloquine should not be used by persons involved with activities requiring fine coordination and spacial performance such as airline crews, and persons using heavy or dangerous equipment. In addition, there is some evidence to suggest that the incidence of serious adverse effects is greater at therapeutic doses of 1000mg and above. It is recommended, therefore, that a maximum of 15mg/kg or a total of 1000mg, whichever is lower, be advised for travellers using mefloquine for emergency self treatment, and that such users should seek medical advice as soon as they are able. Self treatment with a 15mg/kg single dose of mefloquine is not endorsed by the pharmaceutical company.

5.3. The future

5.3.1. Research

The following research topics were identified:

- (i) Identification of the spectrum of neurological and psychiatric reactions to mefloquine
- (ii) Development of standard case definitions for these adverse effects, based on existing WHO adverse reaction terminology
- (iii) Determination of the frequency of neuropsychiatric reactions

- (iv) Identification of risk factors, if any, for these adverse effects
- (v) Definition of the relationship between adverse effects and the pharmacokinetics of mefloquine

5.3.2 MAP/WHO surveillance of adverse events to antimalarials

More information is clearly required on adverse events both to mefloquine and other antimalarial drugs. MAP/WHO is developing methodologies to assess the type, frequency and impact of such adverse events. It is developing a collaborative international approach to the monitoring of adverse events by calling for case reports from the pharmaceutical companies, national drug registers, research institutions and medical practitioners. A standardised case report form will be used to ensure comparable data are collected. These studies will be carried out in collaboration with WHO's programme of International Drug Monitoring.

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TABLE 1: THE SPECTRUM OF NEUROLOGICAL AND PSYCHIATRIC REACTIONS ATTRIBUTED TO MEFLOQUINE

MILD:	Ataxia Fatigue/asthenia Headache Nausea and vomiting Diarrhoea Anorexia Dizziness Dysequilibrium Poor concentration Memory disturbances Sleep disturbances
MODERATE:	Vertigo Logorrhoea Blurred vision Vertigo Anxiety Depression Abnormal neurological coordination Agitation/confusion
SEVERE:	Major depression Anxiety neuroses Suicidal tendencies Seizures Hallucinations Acute psychoses: delusion, paranoia Mutism Manic behaviour, delirium Disturbed consciousness: stupor, coma

TABLE 2: REPORTS OF NEUROLOGICAL AND PSYCHIATRIC REACTIONS FOLLOWING MEFLOQUINE TREATMENT IN CLINICAL TRIALS

DATE OF STUDY	TYPE OF STUDY	COUNTRY	PATIENT Sex *	SYMPTOMS	ONSET (day)	DOSE OF MEFLOQUINE
1980	Phase II	Zambia	M	Confusion, disorientation	2	1000 mg
1981	Phase III	Zambia	M	Restless, uncooperative	9	1000 mg
1982	Phase III	Zambia	M	Awake, unresponsiveness to verbal commands	1	1000 mg
1983	Phase II/III	Thailand	M	Hearing difficulty Severe dizziness	-	500 mg
1983	Phase II/III	Thailand	M	Seizure, psychosis hallucinations	21	1000 mg
1983	Phase II/III	Thailand	M	Acute psychosis	1	2000 mg**
1983	Phase II/III	Thailand	M	Acute psychosis	1	750 mg
1988/89	Phase II/III	Thailand	M	Confusion	1	750 mg
1988/89	Phase II/III	Thailand	M	Hallucinations	5	1250 mg

* M = Male; F = Female

** Received by mistake 2 doses of mefloquine of 1000 mg each at an interval of 52 hours - acute symptoms developed 20 hours after the second dose

**TABLE 3: REPORTS OF NEUROLOGICAL AND PSYCHIATRIC REACTIONS WITH MEFLOQUINE/
SULFADOXINE/PYRIMETHAMINE IN CLINICAL TRIALS**

DATE OF STUDY	TYPE OF STUDY	COUNTRY	SYMPTOMS	ONSET (day)	DOSE (No. of tablets*)
1983	Phase II/III	Zambia	Acute anxiety** subjective amnesia	2	2
1983	Phase II/III	Zambia	Anxiety, depression	1	2
1985	Phase II/III	Zambia	Restless, palpitations	1	2
1985	Phase II/III	Zambia	Hallucinations	?	2
1988/89	Phase II/III	Thailand	Paranoid delusion	5	3

* each tablet contains 250 mg mefloquine/500 mg sulfadoxine/25 mg pyrimethamine

**Follow-up showed this patient was under severe mental stress prior to his attack of malaria

TABLE 4: NEUROLOGICAL AND PSYCHIATRIC REPORTS TO WHO FOLLOWING INDIVIDUAL TREATMENT WITH MEFLOROQUINE (M) OR MEFLOROQUINE/SULFADOXINE/PYRIMETHAMINE (MSP)

COUNTRY	PATIENT Sex* Age (yrs)		TREATMENT	SYMPTOMS	ONSET (day)
France	M	48	1500 mg M	Megalomania	6
France	M	35	1500 mg M	Paresthesia	1
France	M**	56	3 tablets MSP	Severe amnesia, word repeating	4
France	M	22	1500 mg M	Paresthesia	2
France	M	19	1500 mg M	Seizures	2
France	M	20	1500 mg M	Seizures	15
France	M	22	1500 mg M	Seizures	3
France	M	55	1500 mg M	Seizures	7
France	F	5	20mg/kg M	Seizures	21
Thailand	M	18	3 tablets MSP	Depression, hallucination	2
Thailand	M	32	1000 mg M	Depression, suicidal	10
Thailand	M	30	3 tablets MSP	Affective disorder, logorrhoea,	3
The Netherlands	M	56	1250 mg M	Psychotic hallucinations	2
The Netherlands	F	34	1250 mg M	Psychotic hallucinations	3

* M = Male; F = Female

** Patient received quinine for 4 days prior to MSP; symptoms severe.

TABLE 5: TEMPORAL ASSOCIATION BETWEEN MEFLOQUINE INTAKE AND ONSET OF REACTIONS

I. THERAPY

<u>Time of onset (after last dose)</u>	<u>Seizure cases</u>	<u>Psychiatric cases</u>
< 24 hours	3	2
1 day	1	6
2	-	9
3	-	4
6	-	1
7	1	-
8	-	1
9	-	1
10	-	1
16	1	-
19	1	-
21	-	1
Unknown	-	2
TOTAL	7	28

II. PROPHYLAXIS

<u>Number of weeks tablets taken prior to onset</u>	<u>Seizure cases</u>	<u>Psychiatric cases</u>
1	4	4
2	2	2
3	5	4
4	-	-
5	-	1
6	-	2
7	-	-
8	-	1
Unknown	-	2
TOTAL	11	16

TABLE 6: PREVIOUS NEUROLOGICAL OR PSYCHIATRIC HISTORY OF CASES WITH REACTIONS TO MEFLOQUINE

I. REACTIONS REPORTED FOLLOWING THERAPY

	<u>Seizures</u>	<u>Psychiatric</u>
Previous history:		
Yes	-	1
No	7	6
Unknown	-	21
TOTAL	7	28

II. REACTIONS REPORTED FROM PROPHYLAXIS

	<u>Seizures</u>	<u>Psychiatric</u>
Previous history:		
Yes	3	2
No	7	6
Unknown	1	8
TOTAL	11	16

TABLE 7: PREVIOUS OR CONCURRENT ANTIMALARIAL INTAKE BY CASES WITH REACTIONS TO MEFLOQUINEI. REACTIONS RESULTING FROM THERAPY

<u>Previous or co-medication</u>	<u>Seizures</u>	<u>Psychiatric</u>
None	1	3
Chloroquine	2	7
Quinine	-	-
Chloroquine + quinine	2	1
Fansidar ^R + chloroquine + quinine	1	-
Fansidar ^R	1	8
Other (unspecified)	-	1
Unknown	-	8
TOTAL	7	28

II. SIDE EFFECTS RESULTING FROM PROPHYLAXIS

<u>Previous or co-medication</u>	<u>Seizures</u>	<u>Psychiatric</u>
None	6	5
Chloroquine	1	1
Quinine	-	-
Chloroquine + quinine	1	-
Fansidar ^R + chloroquine + quinine	1	-
Fansidar ^R	-	-
Other	1	3
Unknown	1	7
TOTAL	11	16

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