Neuropsychiatric effects of antimalarial drugs

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Neuropsychiatric effects of antimalarial drugs

Neuropsychiatrische effecten van geneesmiddelen tegen malaria

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Op een gegeven moment kon ik het niet meer zien
het was soms verdwenen
net niet te bereiken
totdat zij kwam

Willem de Roon

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1

General introduction

1

General introduction

Malaria is a serious, potentially life threatening disease, and generally endemic in the (sub) tropics. Prevention may be carried out by interrupting transmission, by vector control and by giving travellers prophylactic drugs. The use of prophylactic drugs has generally been effective for both travellers and local inhabitants. However, due to the increase in resistance of *P. falciparum* against the available agents, the prevention of malaria is complicated.

The increase in international travel from temperate to tropical areas and the increase in resistance of *P. falciparum* against the available agents, has led to the development of mefloquine, an effective drug for both the prevention and treatment of malaria (1-3). Mefloquine was introduced in 1985 for the prevention and treatment of malaria tropica. The first mefloquine-related neuropsychiatric adverse effects were reported in the literature in 1989 (4-7). Two years later, the incidence of serious adverse effects was estimated to range between 1:2000-10000 in prophylactic users and 1:250-1754 in therapeutic users (8, 9). Unfortunately, neuropsychiatric reactions to mefloquine remained a vigorously debated topic. Therefore, the studies in this thesis were started, employing all available tools in drug safety research. To gain more insight in the pattern, risk factors and incidence, we began with a review of the literature and a drug utilisation study, studied individual case-reports and case-series and performed both cohort and case-control studies. Finally, we performed a prospective randomised, double-blind clinical trial to demonstrate that our findings were not confounded and that a safer alternative is available. A short introduction to each chapter is giving in the following paragraph.

First, an outline of the problem is given in chapter 2 with a review of the problem and a utilisation study on malaria prophylaxis. As described in chapter 3, the Inspectorate for Health Care in the Netherlands received a total of 136 reports of neuropsychiatric effects attributed to the intake of mefloquine in a prophylactic dose of 250 mg weekly during the period 1992-1995. Because of the invariable occurrence of underreporting, the true incidence of neuropsychiatric adverse effects might be higher than the previously suggested.

Chapter 4 describes a cohort study conducted within subjects travelling to destinations in Africa, Asia, South America and the Middle East. This study suggested that neuropsychiatric adverse effects occurred more frequently in travellers using mefloquine than in users of proguanil or travellers not taking any antimalarial prophylaxis. In chapter 5 a nationwide case-control study is described in which we estimated the risk of serious psychiatric symptoms during the use of mefloquine. In chapter 6 a cohort study is described, in which several potential risk factors for neuropsychiatric adverse events are suggested. In addition, the relationship between serum levels of mefloquine and the occurrence of neuropsychiatric adverse events is studied. In chapter 7 the results are presented of a Phase III clinical trial comparing the occurrence of neuropsychiatric adverse events during the use of a new prophylactic agent, Malarone (atovaquone plus proguanil) and mefloquine. Finally, in the general discussion, the main findings are presented and some methodological issues, clinical relevance of the findings and recommendations for further research are discussed.

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2

Malaria: disease, treatment and prophylaxis

2.1

Malaria: disease, treatment and prophylaxis

Background

Malaria is considered as the most important infectious disease in the world. Approximately 2.1 billion people live in malaria-endemic areas giving rise to 100-300 million cases of malaria per year. Human malaria is caused by infection with sporozoa of the genus *Plasmodium*, that are transmitted by the *Anopheles* species mosquitoes. Four plasmodium species are responsible for the occurrence of malaria:

1. *Plasmodium falciparum* (falciparum malaria)
2. *Plasmodium vivax* (vivax malaria)
3. *Plasmodium malariae* (quartan malaria)
4. *Plasmodium ovale* (ovale malaria)

Of all cases of malaria, falciparum malaria accounts for 40-60% and vivax malaria for 30-40% of the cases. Quartan and ovale malaria are far less common. Falciparum malaria is primarily a disease of the tropics, as is ovale; quartan malaria occurs relatively often in the subtropics and temperate zones, and vivax malaria is more commonly seen than all other types of malaria in the temperate zones, but occurs also in the tropics (1-4,9).

Life cycle of *Plasmodium* species

The *Plasmodium* genus of protozoal parasites has a life cycle, which is split between a vertebrate host and an insect vector. The insect vector is always a female Anopheline mosquito (while males do not feed on blood).

Malaria is transmitted to humans by a bite of a female Anopheline mosquito that bites from dusk till dawn. The life cycle begins in the insect when the female mosquito ingests human blood containing gametocytes. In the stomach of the insect the male gametocyte (microgametocyte) undergoes a process of maturation, during which the microgametes appear. The extrusion of these

spindle-shaped gametes is called exflagellation. The female (macrogametocyte) matures to become a macrogamete.

Male and female gametes fuse, forming a zygote. The zygote becomes elongated and active and is called an ookinete. The ookinete penetrates through the stomach wall of the mosquito and rounds up just beneath the outer covering of the stomach to become an oocyst. The nucleus undergoes mitotic division to produce large numbers of infective parasitic forms, the sporozoites. After a mean of 10 days, the sporozoites invade all parts of the mosquito, some reaching the salivary glands.

The mosquito injects sporozoites from the salivary gland into the human, that rapidly pass into the blood stream (primary exoerythrocytic schizogony). This pre-erythrocytic phase develops in the parenchymatous cells of the liver. On entering the cell the sporozoite rounds up and the nucleus undergoes repeated division. In the course of 6-16 days, the schizont matures and divides to produce small single-nucleated merozoites. The liver cell ruptures and merozoites go either into the blood stream where they invade erythrocytes. During the next 48 hours (*P. falciparum, P. vivax, P. ovale*), or 72 hours (*P. malariae*) each merozoit develops from a ring to a trophozoite and finally to a mature erythrocytic stage schizont with 30-35 merozoites or into contiguous liver cells where they may initiate a secondary exoerythrocytic phase. In falciparum infections no secondary infection of the liver cells occurs, but in other infections this takes place and the liver phase persists. These persistent mononuclear stages of parasites are called hypnozoites and are considered to be dormant. Hypnozoites may be the cause of relapse because development of hypnozoites may produce merozoites of which some enter the blood and infect erythrocytes.

When merozoites have invaded the erythrocytes, the asexual cycle proceeds. The parasites grow within the erythrocyte producing small masses of chromatin, which function as nuclei, and a large central vacuole in the cytoplasm, leading to a so-called ring form. The cytoplasm becomes amoeboid to form the single-nucleated trophozoite. The haemoglobin of the erythrocyte is metabolised, forming insoluble malaria pigment (haemozoin). The trophozoite grows rapidly and the nucleus divides by mitosis until a mature schizont is formed. The erythrocyte ruptures releasing merozoites. Each of the merozoites can reinvade an erythrocyte initiating the cycle of amplification, rupture, and reinvasion that leads to increasing levels of parasitaemia and the pathological and clinical

manifestations of malaria. Clinical manifestations only occur after rupture of infected erythrocytes, which is in general 10-14 days after an individual is bitten by the infected mosquito.

Some of the parasites within the infected erythrocytes do not develop to erythrocytic stage schizonts, but become sexual forms of the parasite, the male and female gametocytes. Before gametocytes are produced, several generations of schizogony have taken place. If a mosquito ingests blood infected with gametocytes, the gametocytes develop during an average of 14 days to sporozoites that can be inoculated into other humans (1-4)

Relapses and recrudescensces

A relapse is a renewed manifestation of malaria due to parasites in the blood which derive from merozoites from a persistent liver phase or from hypnozoites and can only occur in vivax malaria, ovale malaria or quartan malaria. A recrudescence (a renewed manifestation of malaria, subsequent to the primary attack) occurs in falciparum malaria and is due to either a new infection or to multiplication of existing erythrocytic phase parasites (1).

Diagnosis

Pathological changes and clinical signs are caused by erythrocytic phase parasites. There are no pathological or clinical symptoms or signs associated with the presence of hypnozoites or gametocytes. Falciparum malaria is potentially life threatening. All other types are largely self-limited and seldomly lead to death (1-4).

Clinical diagnosis

In case of malaria, the patient will complain of headache, fever, and generalised myalgia. Furthermore, diarrhoea and abdominal pain are sometimes present. Spleen and liver are often palpable. Severe or complicated infections are accompanied by impaired consciousness, weakness, and jaundice. Other complications, which may occur alone or in combination are cerebral malaria, generalised convulsions, normocytic anaemia, haemoglobulinurea, renal failure, hypoglycaemia, electrolyte and acid-base disturbances, pulmonary oedema,

shock, circulatory collapse, hyperpyrexia, hyperparasitaemia and disseminated intravascular coagulation.

Prodromal symptoms are common in all malaria and include depression, severe headache, backache, diarrhoea, nausea and irregular attacks of coldness and shivering. The onset of the primary attack is accompanied by a rise in body temperature (fever) with flushed or pale moist skin. In vivax malaria, fever is irregular at first and may remain irregularly remittent or intermittent.

There are three well-defined stages: the cold, hot and sweating stage. The cold stage begins with a sharp rise of body temperature (40°C) and feelings of intense cold and shivering. The cold stage lasts about 1 hour and is abruptly replaced by the hot stage. The hot stage resembles the symptoms of any other infectious diseases and lasts for 2-6 hours. During this stage, the patient complains of headache, the skin flushes, respiration is rapid and blood pressure falls. The patients is restless, excited and euphoric and may become disorientated or pass into delirium and coma. The hot stage is succeeded by the sweating stage. Just before the sweating stage starts, the temperature falls and becomes normal within an hour or two. As the temperature falls, the patient feels exhausted but relieved and commonly falls into a deep refreshing sleep.

The occurrence of fever corresponds roughly with the rupture of schizonts and liberation of merozoites, pigment and debris into the blood stream.
In *P. falciparum, P. vivax* and *P. ovale* schizogony takes 48 hours resulting in a febrile paroxysm occurring every third day (tertian periodicity). In *P. malariae,* schizogony takes 72 hours resulting in a febrile periodicity once every fourth day. During these intervals, the temperature remains normal and the patient feels well. Complaints occur whenever the next paroxysm starts. The duration of the attack depends on the species of the parasite and the immune status of the patient. The first attack of P. *falciparum* in a non-immune subject usually lasts short (less than a few weeks) but mostly ends fatal without treatment. Primary attacks caused by other species may last for weeks to several months but are generally not fatal. However, these self-limiting forms of malaria are commonly followed by relapses.

Falciparum malaria is categorised into uncomplicated and severe falciparum malaria. Complications (severe falciparum malaria) usually appear in the late stages of an attack (either untreated or repeated inadequately treated attacks).

Severe falciparum malaria includes hyperparasitaemia (>5% of the erythrocytes infected) accompanied by the complications mentioned above (1-5, 9).

Parasitological diagnosis

The usual laboratory tests are non-specific. Leukocyte and platelet counts are often decreased. Indirect bilirubinemia and a mild increase in serum glutamic oxaloacetic transaminase and lactic dehydrogenase may occur. Proteinuria is seen in patients with the nephrotic syndrome and haemoglobine and hematocrit will be decreased in patients with severe infections. Furthermore, mild elevations of blood urea nitrogen and creatinine may be seen secondary to dehydration.

The most reliable diagnosis of malaria is made by a peripheral bloodsmear. The examination of stained thick blood films is sufficient for the diagnosis of the presence of asexual parasites. Using this technique, distinction between infection with *P. falciparum* and other parasites can be made. Stained thin blood films are used to differentiate between infections with *P. vivax, P. ovale* and *P. malariae.*

Thick films are prepared by placing a drop of blood from a needle prick in a finger or ear lobe on to a clean glass microscope slide and spreading it evenly over a circular area about 2 cm across. The film is stained by immersion in Giemsa's stain or Field's stain. Under the microscope, the cytoplasm of the parasites stain blue and the nuclear chromatin reddish purple. Thin films are prepared and stained with Giemsa's stain or Leishman stain. Differentiation of the infecting species depends on the appearance of the parasites.

Repeated examinations (morning and evening) should be done in case of suspected malaria. Repeated examinations are particularly important in malaria falciparum because the number of parasites in the blood vary considerably over the day.

It is important to differentiate the type of malaria, because most malaria associated complications and deaths are caused by *P. falciparum*. Furthermore it is important, since infections with *P. ovale* or *P. vivax* require treatment to eliminate hypnozoites from the liver, that will prevent relapses.

The percentage of erythrocytes with parasites should be determined. The patient is diagnosed with severe malaria if more than 5% of the erythrocytes has parasites (1-5,7, 9).

Treatment

The treatment of malaria depends on the severity of the infection (severe or uncomplicated malaria), age and degree of immunity of the patient, and susceptibility of the pathogen to antimalarial drugs. Drugs used in the treatment are either active against the erythrocytic forms, offering clinical cure (Chloroquine, quinine, pyrimethamine), or active against the exoerythrocytic forms (primaquine) resulting in complete elimination of the pathogens (1-4, 6).

Drugs used in the treatment of malaria

Drugs used in the treatment of malaria can be classified into two groups. The first group is characterised by their rapid schizontocidal action and include chloroquine, quinine, mefloquine and primaquine. Primaquine is less active against the erythrocytic forms than the others.

The second group, including pyrimethamine and sulphonamides, is characterised by a schizontocidal effect that is slow in onset and dependent on the stage of multiplication of the parasites. Pyrimethamine acts by inhibiting dihydrofolate reductase. By inhibiting dihydrofolate reductase, the formation of tetrahydrofolate is inhibited that is required for DNA synthesis. These agents have a greater affinity for the plasmoidal enzyme than for the human enzyme. Sulphonamides inhibit the synthesis of folate by competing with para-aminobenzoic acid for dihydropteroate synthetase. They are active against the erythrocytic forms of plasmodia but not against the sporozoite or hypnozoite forms. They are never used alone, only in combination with pyrimethamine, resulting in sequential blockade, and a synergistic effect (1-4,6,7, 11).

Treatment of *P. falciparum*

P. falciparum was originally sensitive to chloroquine, however, strains resistant to this and other antimalarial drugs are emerging. Cases of uncomplicated malaria (where patients can take oral therapy) can be treated with several regimens (table 1 and 2). When treated with quinine, patients will usually develop 'cinchonism' (tinnitus, high-tone hearing loss, nausea, dysphoria) after 2-3 days but should be encouraged to complete the full course to avoid recrudescence. When treated with mefloquine, antipyretic and anti-emetic agents may need to be given prior to mefloquine administration to reduce the risk of

vomiting. If nausea and vomiting preclude oral therapy, quinine can be given intravenously until the patient can take medication orally.
In case of severe malaria (coma, jaundice, renal failure, hypoglycaemia, acidosis, severe anaemia, high parasite count, hyperpyrexia), the patient is ideally treated in an intensive care or high dependency unit and monitored both clinically and biochemically. Intravenous quinine is the treatment of choice. However, rapid injection can lead to hypertension, dysrhythmias and eventually death (1,3-7,11).

Treatment of *P. vivax*, *P. ovale* and *P. malariae*

Most strains of P. vivax are sensitive to chloroquine although some chloroquine resistant strains have been reported in Papua New Guinea, Indonesia, Thailand and India.

Chloroquine will clear the erythrocyte stages of the parasite but it has no effect on the exo-erythrocytic liver stage and a course of primaquine is required for radical elimination. If primaquine is not given, the patient may suffer a relapse, which will occur weeks or months after the original attack. Primaquine is preferably started after chloroquine. The advised dose of primaquine is 3 mg base/kg divided over 14 days. When the infection is acquired in South-East Asia, 6 mg base/kg of primaquine should be given divided over 14-21 days (with a maximum of 30 mg base per day). Usually, the dose of primaquine is 15 mg base per day with a duration of 14 days. When the infection is acquired in South-East Asia 22,5 mg base per day should be administered with a duration of 21 days. When a relapse occurs both chloroquine and primaquine treatment should be repeated. Before the parasite is finally eliminated, up to three relapses may occur.

Before primaquine is prescribed, patients should have their G6PD status checked Patients with G6PD deficiency may undergo haemolysis if they use primaquine and it is recommended that these patients be given 30-45 mg once a week for 8 weeks. Treatment for the eradication of *P. ovale* and *P. malariae* is the same as that for *P. vivax* except that it is not necessary to prescribe primaquine to patients with P. malariae infections (1,3-7, 11).

Table 1 Treatment of malaria

Infection		Drug	Route of administration	Length of treatment
P. falciparum	Severe	Quinine	IV infusion	3-7 days
		Artemether	IM	24-48 hours
		Chloroquine	IV infusion/IM/SC	36 hours
		Artesunate	IV / IM	max 7 days
	Uncomplicated	Chloroquine	Oral	48 hours
		Pyrimethamine/ sulfadoxine	Oral	Single
		Quinine	Oral	7 days
		Mefloquine	Oral	24 hours
		Doxycycline	Oral	7 days
		Halofantrine	Oral	18 hours
P. vivax		Quinine	IV infusion	3-7 days
P. ovale	Severe	Arthemeter	IM	24-48 hours
P. malariae		Chloroquine	IV/infusion/IM/SC	36 hours
	Uncomplicated	Chloroquine	Oral	48 hours
		Mefloquine	Oral	Single
		Pyrimethamine/ sulfadoxine	Oral	Single
		Halofantrine	Oral	18 hours
P. vivax		Primaquine	Oral	14-21 days
P. ovale	radical cure			

Table 2 Dose and regimen of treatment

Infection		Drug	Initial dose (mg/kg)	Other doses (mg/kg)	Interval (hours)
P. falciparum	Severe	Quinine	20 (salt)	10	8
		Arthemeter	3.2	1.6	24
		Chloroquine	0.83 mg/kg/h	-	-
		Artesunate	2.4	1.2	2x12, 24
	Uncomplicated	Chloroquine	10 (base)		12
			10 (base)	10, 5 (base)	24
		Pyrimethamine (P)/ sulfadoxine (S)	20 S + 1 P	-	-
		Quinine*	10	10	8 (7 days)
		Mefloquine	15 (base)	10 (base)	8-24
		Doxycycline	3	3	24
		Halofantrine**	8	8	6
P. vivax		Quinine	20	10	8
P. ovale	Severe***	Arthemeter	3.2	1.6	24
P. malariae		Chloroquine	0.83	-	-
		Artesunate	2.4	1.2	2x12, 24
	Uncomplicated***	Chloroquine***	10 (base)	5 (base)	12
			10 (base)	10, 5 (base)	24
		Mefloquine***	3	3	24
		Halofantrine***	8	8	6
P.vivax					
P.ovale	radicale cure	Primaquine	15-30 mg per day	15-30 mg per day	24

* In combination with P+S : 3 days. In combination with tetracycline, doxycycline, or clindamycine 7 days

** Retreatment after 7 days *** Radical cure of P.vivax and P. ovale in combination with primaquine

Prevention

The risk of acquiring malaria during travel must be estimated before departure. The risk depends on the level of transmission (place and season), duration of stay (especially rural areas), hours of mosquito contact, prevalence of chloroquine resistance, availability of treatment, and associated medical conditions. Prevention is divided into two categories, the general protective measures and chemoprophylaxis (1,3,4,10,15).

General protective measures

Travellers should take active measures to protect themselves against mosquito bites. The mosquito generally bites from dusk to dawn, therefore, just before dusk clothing should be worn that covers the arms and legs. In addition a mosquito repellent containing N,N-diethyl-meta-toluamide (DEET) should be applied on all parts which are not covered. It is advised to sleep under an impregnated mosquito net in a room free of mosquitoes. The WHO advises to impregnate mosquito nets with permethrine, deltamethrine or other pyrethroids. These agents have insecticide and in case of permethrine mosquito repellent actions (3,10,14,15).

Chemoprophylaxis

Drugs used for chemoprophylaxis block the link between the exo-erythrocytic stage and the erythrocytic stage and thus prevent the development of malarial attacks. True chemoprophylaxis (e.g. the prevention of infection by killing the sporozoites on entry into the host) is not achieved with the drugs at present use but may be achieved when vaccines become available. Prevention of the development of clinical attacks can be effected by chemoprophylactic drugs that kill the parasites when they emerge from the liver after the pre-erythrocytic stage. It is important that the use of chemoprophylactic drugs is started before entering the endemic area (this run-in period depends on the type of drug) and is continued throughout the stay and at least one month after leaving this area. The choice of drug is difficult as factors which are included in the decision are: do potentially serious adverse effects weigh against the risk of acquiring malaria, what is the pattern of resistance in the particular area, what is the level of transmission in this season and area and what is the risk of exposure of the individual to mosquito bites. No chemoprophylactic regimen is 100% effective

and besides the use of chemoprophylactic drugs other preventive measures (as described in the previous section) should be taken (3,4,10,14,15,19).

Chloroquine

Chloroquine is a 4-aminoquinoline. The drug is active against the asexual forms of human pathogenic malaria parasites. Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract. It is active against the erythrocytic stages of the parasite life-cycle. It is, however, inefficient against gametocytes or exo-erythrocytic liver forms. It is said to cause fragmentation of the parasite RNA, and to be able to intercalate in the DNA of the parasite. Furthermore, chloroquine inhibits digestion of haemoglobin by the parasite and reduces the supply of amino acids necessary for parasite viability. Chloroquine is accumulated to high concentrations selectively within parasitised erythrocytes and this accumulation is essential to antimalarial activity. It undergoes extensive metabolism in the liver and is slowly eliminated from the body (6,10,12,13,14).

Dosage

In the Netherlands, chloroquine is prescribed only in combination with proguanil. The recommended dosage for adults is 300 mg chloroquine base per week. The prophylaxis is started with 300 mg on two consecutive days, followed by 300 mg per week. Prophylaxis with chloroquine starts at the day of entry of the endemic area and is continued for at least four weeks after leaving this area. Chloroquine is recommended for malaria prophylaxis during pregnancy. It is excreted in small amounts into breast milk, but it can nevertheless be taken during the nursing period (12,14-16).

Adverse effects

Oral chloroquine is well tolerated. Frequently occurring adverse effects are: pruritus, nausea and vomiting, loss of appetite, abdominal cramps, diarrhoea, headache, sleep disturbances, dizziness, fatigue, and reversible deposition of chloroquine in the cornea resulting in blurred vision and disturbance of accommodation. It may aggravate psoriasis, especially in patients with light-sensitive disease. Photosensitization, aplastic anaemia, agranulocytosis, myopathy and psychiatric disturbances may occur. The most serious adverse effect of chloroquine is irreversible retinopathy, which may occur during long

term use but has rarely been attributed to chloroquine used for malaria prophylaxis.
Long-term chloroquine therapies can also lead to myopathy, skin, hair and nail alterations, pigmentation of the hard palate, and less frequently to neuropsychiatric complaints (e.g. convulsions), ECG alterations, impairment of the blood production, and photosensitization (4,6,10,12,14-16,19).

Mefloquine

Mefloquine, a quinolinemethanol, is related to quinine and active as a rapid-acting blood schizontocide against all species of human malaria. It interferes with the transport of haemoglobin and other substances from the erythrocytes to the food vacuoles of the malaria parasite. Mefloquine only has an effect on the asexual forms of the parasite in the blood (blood schizontocidal effect). There is no effect on the exoerythrocytic liver forms or on the gametocytes. Mefloquine is well absorbed from the gastrointestinal tract and has a large volume of distribution, indicating that it is extensively tissue bound. In plasma it is for 99% bound to protein. Mefloquine undergoes hepatic biotransformation, and only 5% of the oral dose is excreted unchanged into the urine. The elimination half-life is approximately 3 weeks (4,6,12,17,18).

Dosage

The recommended dose of mefloquine for adults is 250 mg once weekly. Chemoprophylaxis with mefloquine should start three weeks before entering the endemic area and must be continued for four weeks after leaving this area (14,15).

Adverse effects

Adverse reactions to mefloquine are mostly dose dependent. Vertigo or imbalance, light-headedness, nausea, vomiting, abdominal pain, and diarrhoea are relatively common. Sinus bradycardia also occurs. Pruritus and skin rashes have been observed but they are rare. Neuropsychiatric symptoms may occur. In addition to actual psychoses with excitation, confusion or hallucinations, depression, sleep disturbances, convulsions, ataxia, headache and visual and auditory disturbances have been observed (4,6,12,14,17,18).

Contraindications

Because mefloquine prolongs cardiac conduction, mefloquine is not recommended for patients taking β-blockers, quinine or quinidine. Other contraindications are a history of epilepsy or psychiatric disorder and pregnancy. Mefloquine is teratogenic in high doses in animals and potentially also in humans. Women of childbearing age should not become pregnant during chemoprophylaxis with mefloquine until three months after the last dosage of mefloquine. Particular caution is indicated in subjects for whom spatial discrimination and fine co-ordination are important. (4,2,14,15,17,18)

Proguanil

Proguanil is a dihydrofolate reductase (DHFR) inhibitor, which is a prodrug and is converted to the active compound cycloguanil by the mixed function oxidase system of the liver. Cycloguanil acts as a competitive inhibitor of DHFR and the effect on the malaria parasite is to reduce the biosynthesis of folate, resulting in decreased synthesis of pyrimidines and blockage of DNA replication. Proguanil is well absorbed and peak plasma concentrations are achieved within 4 hours after oral administration. The half-life is approximately 12 hours. (10,12-14).

Dosage

The recommended dose for adults is 200 mg daily. Chemoprophylaxis with proguanil is started at the day of entry of the endemic area and is continued at least four weeks after leaving this area. The drug has been shown to be safe in pregnancy (10,12,14,15).

Adverse effects

Proguanil has been considered to be one of the best-tolerated antimalarial agents. No fatal adverse reactions have been reported. Frequently occurring adverse effects are gastrointestinal distress, aphthous ulcers and nausea (10,12,14).

Doxycycline

Doxycycline is a tetracycline derivative, which is used as an alternative to mefloquine for short-term travel in areas where chloroquine resistant *P. falciparum* is endemic. It attacks both the pre-erythrocytic phase and the erythrocytic phase of the Plasmodium life cycle by binding to ribosomes and

thus inhibiting the protein synthesis. It is well-absorbed (90-100%) and protein bound. The half-life is 12-22 hours. Doxycycline is partially inactivated by hepatic metabolism and approximately 35% is excreted unchanged in stool or urine (8,10-12,14).

Dosage

Doxycycline is taken in a dosage of 100 mg per day, starting the day of entry of the endemic area and is continued for four weeks after the traveller has left this area (10, 14,15).

Adverse effects

The most common adverse effects of doxycycline are gastrointestinal disturbances, photosensitivity, nausea, esophagitis, and vaginal candidiasis. Abdominal pains and diarrhoea are less common; very rarely a pseudomembranous colitis can occur (10,12,14,19).

Contraindications

Doxycycline is contraindicated in pregnant women and children less than 8 years old. It causes disturbances in the development of the teeth and bones of the fetus and in children staining of the teeth and possibly disturbed bone growth (10,11,14,15).

Resistance

Resistance to antimalarial drugs has been established in parasites infecting man, monkeys and rodents. The resistance of *P. falciparum* to antimalarial drugs has become a major epidemiological concern. The WHO defined drug resistance as "the ability of a parasite strain to multiply or to survive in the presence of concentrations of a drug that normally destroy parasites of the same species or prevent their multiplication. Resistance may be relative (yielding to increased doses of the drug tolerated by the host) or complete (withstanding maximum doses tolerated by the host)" (21). Resistance is considered to result from spontaneous chromosomal point mutations (independent or drug pressure), followed by selection of the more resistant mutants under drug pressure. Resistance to the DHFR inhibitors can arise from single point mutations,

however, resistance to the quinolines requires a series of unlinked additive mutations.

Antimalarial drug resistance is likely to occur in three sets of circumstances:
1. Large scale antimalarial drug use
2. Inadequate dosing
3. Adequate dosing with drugs that are eliminated slowly from the body.

Inadequate dosing occurs commonly because of poor compliance with treatment regimens or unregulated antimalarial drug distribution and self-prescribing. The greatest pressure occurs in circumstances where the whole population is exposed to low antimalarial drug concentrations.
Slowly eliminated drugs (e.g. mefloquine) persist in the blood at sub-therapeutic concentrations, and act as a selective pressure when the patient is reinfected. Because chloroquine is safe, effective for the treatment of severe malaria, and economical, the development of chloroquine resistant *P. falciparum* is one of the most important factors in the resistance of malaria. The emergence and spread of chloroquine resistant *P. falciparum* leads to a high morbidity and mortality of malaria and has exacerbated the difficulties of treating severe malaria (1,11, 21-23).

Guidelines

As stated in the previous section, antimalarial drug resistance is a major problem in the treatment and prophylaxis of malaria. Because antimalarial drug resistance is likely to occur with large scale antimalarial drug use, with inadequate dosing of these drugs and with adequate dosing with drugs that are eliminated slowly from the body, guidelines for prescribing these drugs are necessary. The first step in preventing antimalarial drug resistance is informing and educating the prescribers about the possibilities of prevention and creating guidelines to which they can adhere. The next step is informing the traveller and stress the need of adherence to these guidelines. In the next section, we describe a study, performed in The Netherlands in which we give insight into the dispensing of malaria chemoprophylaxis and to determine whether health care providers have followed changes in guidelines, from 1993 to 1999.

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2.2

Utilisation of malaria prophylaxis: the effect of changes in guidelines in the Netherlands 1993-1998

Summary

Introduction: The increase in international travel from temperate zones to tropical countries and increasing drug resistance of *P. falciparum* has resulted in a growing number of travellers that are at risk for contracting malaria. The objective of this study is to obtain insight into dispensing patterns of malaria chemoprophylaxis and to determine whether health care providers have followed changes in guidelines.
Methods: Data on prescriptions of proguanil and mefloquine were obtained from the Dutch "Foundation for Pharmaceutical Statistics" (SFK) covering the period January 1st 1993 up to December 31st 1998. From the Statistics Netherlands (SN) we obtained the number of travellers to endemic areas during the years 1994-1998.
Results: There were 420,963 prescriptions for mefloquine and 464,904 for proguanil dispensed during the study period. The total number of prescriptions for malaria chemoprophylaxis increased during the period 1993-1997. The number of prescriptions per 1000 travellers decreased over the years. The average duration for which mefloquine was prescribed remained stable whereas the average duration for which proguanil was prescribed decreased over time. We observed differences in the prescription rate of prescriptions for mefloquine *between* geographical regions in the Netherlands. In 1998 for example, the proportion of prescriptions for mefloquine was 20% higher in region 8 as compared to the reference region.
Conclusion: Changes in the guidelines of malaria prophylaxis with respect to type and duration were followed by health care providers. Nevertheless there are variations between the regions in the proportion of prescribed courses of mefloquine, which may be explained by differences in ethnic background of the inhabitants of these regions.

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Introduction

Malaria is the world's most important parasitic infection. It is primarily caused by *Plasmodium falciparum*, which has been eradicated from the temperate zones but is still the major cause of morbidity and mortality in tropical countries. The increase in international travel from temperate zones to tropical countries and the increased drug resistance of *P. falciparum* has resulted in a growing number of travellers at risk for contracting malaria.

During the past years, guidelines for travellers from the Netherlands who visit malaria endemic areas have changed considerably. In the Netherlands, monotherapy with proguanil is used as a first choice malaria prophylaxis for countries where little or no resistance is reported to either chloroquine or folate inhibitors such as pyrimethamine/ sulphamethoxazole or proguanil. In areas where resistance to chloroquine and folate-inhibitors is reported, monotherapy with mefloquine is generally prescribed as chemoprophylaxis for malaria. In case of contraindications for mefloquine, the usually less effective combination of proguanil and chloroquine is prescribed. Chemoprophylaxis with proguanil or the combination of proguanil and chloroquine has to be started on the day of departure and all regimens needed to be used up to four weeks after leaving the endemic area.

Before 1994 mefloquine was prescribed for a limited number of malaria areas. In 1994, guidelines were changed and the number of areas for which mefloquine was recommended as the drug of first choice, was increased. At that time travellers were advised to start chemoprophylaxis with mefloquine one week before entering the endemic area.

In 1996, the guidelines regarding the use of mefloquine were changed in view of the facts that adverse effects usually appear within 3 weeks and that a number of travellers were not protected during their first few weeks of travel because of insufficient blood levels of mefloquine (1,2). Instead of a one week run-in period, it was advised to start 3 weeks before entering the endemic area.

In the beginning of 1998, the guidelines were changed again, partly because of the publicity about the adverse effects of mefloquine in the Dutch lay press. For short trips, travellers were advised to use the combination of chloroquine and proguanil instead of mefloquine or in some cases not to take any antimalarials at all. At present, the potential adverse effects of antimalarials are weighed against the risk of acquiring malaria. The risk of acquiring malaria

depends on the travel destination (geographic area visited), the behaviour of the traveller, the type of destination (rural/urban), type of accommodation, season, use of non-pharmacological preventive measures and the effectiveness of and compliance with these preventive measures.

In order to give tailored travel advice and to allow a risk-benefit assessment, health care providers need to be properly informed and educated (3-5). In the Netherlands, health care providers are informed through the national guidelines for malaria prophylaxis that are published by the Dutch government and since 1997 by a specialised travel health advice office (National Co-ordination Centre for Travellers Health).

The objective of the present study is to provide insight into the prescription patterns of malaria chemoprophylaxis over the past years, and to assess whether these patterns are consistent with the changes in guidelines.

Methods

Drug Utilisation data

In the Netherlands, antimalarials can only be obtained on prescription. Data on prescriptions of antimalarials were obtained from the Dutch "Foundation for Pharmaceutical Statistics" (SFK). Every three months, the SFK obtains information on all filled prescriptions from approximately 1000 out of the 1515 community pharmacies in the Netherlands. This represents the drug use of 9 million persons (almost two-thirds of the Dutch population). In order to extrapolate this information to the entire Dutch population weights are assigned to each collaborating pharmacy based on the insurance type of the patients and geographic location of the pharmacy. From the database, we obtained data on all dispensed prescriptions of proguanil (ATC: P01BB01) and mefloquine (ATC: P01BA05) during the period January 1st 1993 up to December 31st 1998. Each recorded prescription accounted for a full course of chemoprophylaxis and contained information on ATC code, number of filled tablets or capsules, age category of the user, and geographic location of the pharmacy.

Since there is only one strength available for each of the antimalarial drugs we could calculate the duration of use in weeks. We divided the dispensed number of tablets or capsules by 14 in case of proguanil (7 days, 2 tablets per day), and by 1 for mefloquine (1 tablet per week). From the Statistics Netherlands (SN) we obtained the number of travellers to endemic areas during

the years 1994-1998. The SN collects, interprets and presents statistical information about the Dutch society.

Analyses

In this paper, we describe changes in the absolute number of prescriptions of proguanil and mefloquine over time, changes in type of antimalarial drugs per 1000 travellers to endemic areas over time, the duration of use and differences in the prescription rate of mefloquine between geographic regions. Since there were no changes in guidelines regarding the duration of use of proguanil during the study period, the mean duration of stay could be calculated by subtracting 4 weeks from the mean duration of use since the prescription duration takes into account that the drug should be continued for 4 weeks after leaving the endemic area.

In order to study changes over calendar time we calculated for each of the 23 geographic regions the prescription rate of mefloquine per year by dividing the number of prescriptions of mefloquine by the total number of prescriptions for antimalarial prophylaxis in each year. All proportions were standardised to the proportion of mefloquine prescriptions of region 20 in 1996. Region 20 represents the mean proportion of mefloquine prescriptions in 1996, which is the midpoint of the study period. In order to compare the variation in prescribing in 1998 between the 23 regions in the Netherlands, we calculated the prevalence ratio and 95% confidence limits of the percentage of mefloquine prescriptions by reference to the percentage of mefloquine prescriptions in the region with the lowest proportion of mefloquine use (region 19).

Table 1 Number of prescriptions of malaria prophylaxis

Year	Total # prescriptions	Mefloquine	% of total	Proguanil	% of total
1993	98,325	14,427	(14.7)	83,898	(85.3)
1994	140,226	59,295	(42.3)	80,931	(57.7)
1995	173,895	97,028	(55.8)	76,867	(44.2)
1996	165,055	93,210	(56,5)	71,845	(43.5)
1997	168,452	90,232	(53.6)	78,220	(46.4)
1998	139,914	66,771	(47.7)	73,143	(52.3)
Total	885,867	420,963	(47.5)	464,904	(52.5)

Results

We obtained information on 420,963 prescriptions for mefloquine and 464,904 for proguanil that were dispensed during the study period (table 1).

The number of prescriptions of mefloquine strongly increased from 1993 until 1995, slightly declined in 1996-1997 and more strongly decreased in 1998. The use of proguanil decreased concomitantly with the increasing use of mefloquine in 1994-1995 and slightly increased with the subsequent decrease in use of mefloquine.

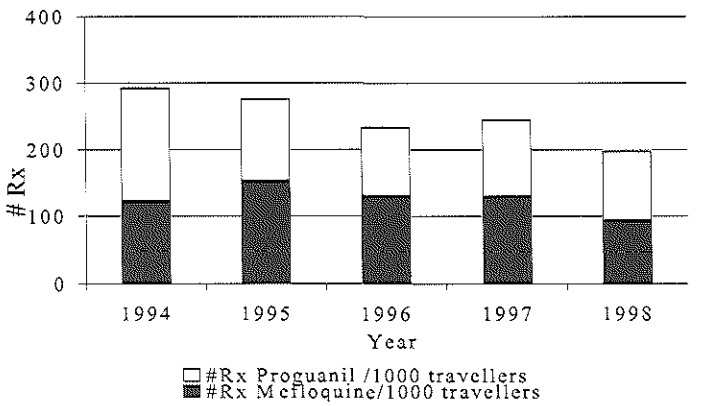

Figure 1 Prescriptions per 1000 travellers

In figure 1 and table 2, we present the total number of prescriptions for antimalarial drugs, and the number of prescriptions for proguanil and mefloquine per 1000 travellers.

Table 2 Number of prescriptions of malaria prophylaxis per 1000 travellers

Year	Number of travellers*	Absolute number of prescriptions of mefloquine	Number of prescriptions of mefloquine per 1000 travellers	Absolute number of prescriptions of proguanil	Number of prescriptions of proguanil per 1000 travellers
1994	480.000	59.295	124	80.931	169
1995	630.000	97.028	154	76.867	122
1996	710.000	93.210	131	71.845	101
1997	690.000	90.232	131	78.220	113
1998	710.000	66.771	94	73.143	103
Total	3.220.000	406.536	126	281.006	118

*approximation

Although the total number of prescriptions for malaria chemoprophylaxis increased from 1994-1997, the number of prescriptions per 1000 travellers decreased over the years (table 2).

The number of prescriptions for proguanil per 1000 travellers decreased from 1994 to 1996 with a small transient increase observed in 1997. The number of mefloquine prescriptions per 1000 travellers increased from 1994 to 1995 and then decreased. Until 1997, the use of mefloquine exceeded the use of proguanil, but in 1998 proguanil was used more frequently. Stratification for age showed the same pattern in all age categories (data not shown). Table 3 shows the duration of mefloquine and proguanil prescriptions and the difference between the duration of the two regimens.

Table 3 Duration (weeks)

Year	Mefloquine	Proguanil	Calculated mean duration of stay	Mean difference duration mefloquine - proguanil
1993	10.36	8.83	4.83	+ 1.58
1994	10.08	8.95	4.95	+ 1.16
1995	9.48	8.72	4.72	+ 0.77
1996	10.12	8.28	4.28	+ 1.78
1997	10.07	7.96	3.96	+ 2.11
1998	10.12	7.32	3.32	+ 2.81
1999	10.37	7.20	3.20	+ 3.22
Total	9.99	8.29	4.29	+ 1.83

The mean duration of a prescription was 8.3 weeks for proguanil and 10 weeks for mefloquine respectively. Figure 2 shows the mean duration of use of mefloquine and proguanil and the difference between the two regimens. Although the duration of mefloquine prescriptions remained stable over time the duration of use of proguanil decreased between 1993 and 1998. The mean difference of duration of prescriptions between mefloquine and proguanil showed an increase from about 1 week in 1994, to approximately 3 weeks in 1998.

Stratification for geographic region and temporal analyses showed no differences regarding the pattern of prescribing of mefloquine *within* the 23 regions. Up to 1996, the proportion of mefloquine increased in every region and from 1997 onwards, the proportion of mefloquine use is decreasing. Figure 3 shows the differences between the regions in 1998, taking region 19 (lowest

prescription rate of mefloquine) as the reference region. The figure shows that physicians in region 8 prescribe mefloquine 20% more frequently. In region 15 and 17 it is approximately 18% higher and region 1, 4 and 13 are comparable with the reference region.

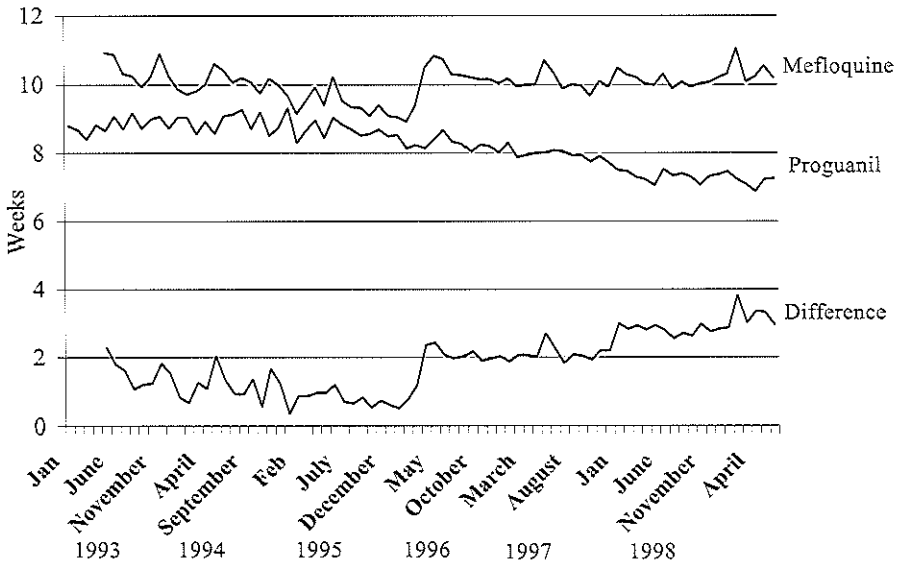

Figure 2 Duration of use of mefloquine and proguanil

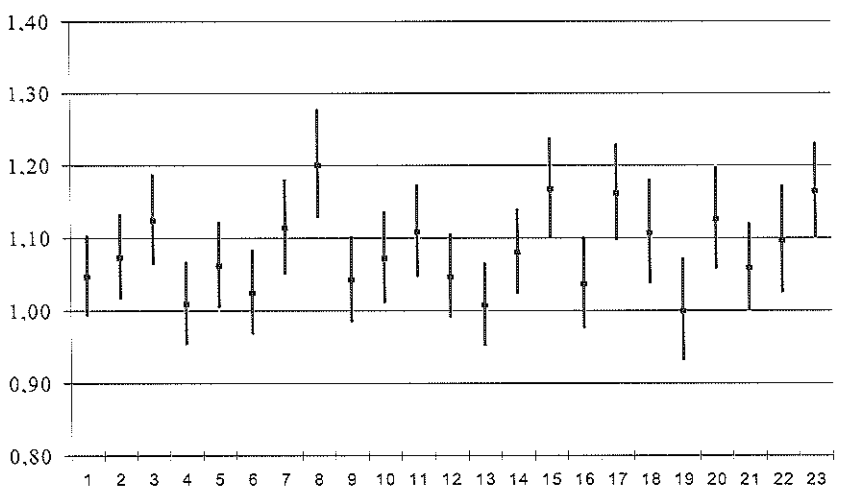

Figure 3 Ratio of prescribed courses of mefloquine and all antimalarial drugs in 23 regions in the Netherlands in 1998

Discussion

In this study, we described the pattern of use of chemoprophylaxis for malaria. According to the Dutch guidelines, prior to 1994, the drug of choice for malaria prophylaxis was proguanil for areas with little or no resistance and mefloquine for areas with chloroquine resistant *P. falciparum*. In August 1994, the first changes regarding the use of mefloquine were implemented (6, 7).

In table 1 and figure 1 it is shown that up to 1994, proguanil was used more frequently than mefloquine but in 1995, the use of mefloquine exceeded the use of proguanil. At that time, two regimens of malaria prophylaxis were advised (i.e. proguanil or mefloquine), depending on the tropical area that was visited.
In March 1996, the guidelines regarding the run-in period for mefloquine were updated. The period of use of mefloquine prior to entering the malaria-endemic area was extended from one to three weeks to ensure an effective blood level and to increase the chance of detecting possible adverse effects before departure (8, 9). We observed that in line with the changes, the difference in mean duration of use between proguanil and mefloquine increased (figure 2).

Until 1997, the mean difference of duration of use between proguanil and mefloquine ranged from 0.77 to 1.78 weeks, which is compatible with the advice at that time to start mefloquine one week before entering the endemic area, and to start proguanil on the day of entering the endemic area. The change in the guidelines to start mefloquine three weeks before entering the endemic area resulted in a mean observed difference of duration that increased with 2-3 weeks. Apparently, the increase in mean difference is not due to an absolute longer duration of use of mefloquine, because the duration of use of mefloquine remained stable over the years at approximately 10 weeks. Since there were no changes in guidelines regarding the use of proguanil, the mean duration of stay could be calculated by subtracting 4 weeks from the mean duration of use. The duration of use of proguanil diminished over the years leading to the conclusion that the duration of stay in the malaria areas decreased and that the change in guidelines in 1997 to prescribe mefloquine for an extra two weeks before entering the endemic area was followed by the prescribers.

In August 1997, the primary prevention of malaria by taking non-pharmacological anti-mosquito measures such as bed nets and the use of repellents received more emphasis.

The new guidelines emphasise four steps for malaria avoidance (*ABCD*): *A*wareness of the risk, *B*ite avoidance, *C*ompliance with appropriate chemoprophylaxis and early *D*iagnosis of malaria breakthrough. Due to the reported adverse effects, health care providers were instructed to be more cautious in prescribing mefloquine. Mefloquine should be prescribed only when a traveller stayed more than 7 nights in a malaria endemic area for which mefloquine is the first choice prophylactic drug. The combination of proguanil and chloroquine is advised for shorter stays in these areas (10, 11). This advice is reflected in the utilisation data. Until 1997, the use of mefloquine exceeded the use of proguanil, from 1997 onwards proguanil was used more frequently, and the mean duration of use diminished.

The SFK distinguishes 23 regions between which we observed differences regarding the prescription rate of mefloquine. Since we calculated the proportion by taking all prescriptions of chemoprophylaxis per year as our dominator, these regional differences could not be explained by differences in population density. The regional differences are therefore a result of differences in prescription behaviour between physicians and/or differences in travel behaviour between inhabitants.

Being an ecological design, there are some limitations in this study. Mefloquine may be prescribed in a loading dose (3 tablets of mefloquine spread over one week) for travellers who start prophylaxis less than three weeks before entering the endemic area. In this study, we could not distinguish between a regular prescription and a loading dose. Secondly, we could not exactly calculate the number of persons at risk for malaria. From the Statistics Netherlands we obtained the number of travellers to continents that are known to have endemic malaria areas. However, the risk to contract malaria may strongly differ between urban and rural areas within a country, and this difference may be reflected in the choice of antimalarial chemoprophylaxis. Therefore we may have overestimated the number of travellers to actual malaria areas and underestimated the number of prescriptions per 1000 travellers. Furthermore, we obtained data on prescriptions of antimalarials from the SFK representing approximately 1000 community pharmacies. We were not able to obtain data on prescriptions of antimalarials from the 600 drug dispensing general practitioners. Although this is not likely to affect the trends we observed, this may be another reason for underestimating the number of prescriptions per 1000 travellers. The

differences in prescription rates between regions could not be caused by differences in population density of the regions, however, the ethnic background of the inhabitants and travel behaviour may be of importance in explaining the differences between the regions. Due to the ecological nature of the data, we could not examine this effect.

In conclusion, changes in the guidelines of malaria prophylaxis with respect to type and duration were followed by health care providers. Nevertheless small variations were observed between the regions in the proportion of prescribed courses of mefloquine, which may be explained by differences in ethnic background of the inhabitants of these regions.

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3

Spontaneous reports of psychiatric adverse effects to mefloquine

3.1

Spontaneous reports of psychiatric adverse effects to mefloquine in the Netherlands

Summary

Objective: To study all reports of neuropsychiatric effects to mefloquine, notified since 1992 to the Inspectorate for Health Care in the Netherlands.
Method: Descriptive study.
Results: In the period 1992-1995, the Inspectorate received 136 reports of neuropsychiatric reactions attributed to the use of mefloquine, of which 132 could be analysed. It concerned 44 males and 88 females with a mean age of 37 and 35 years respectively. The most important effects consisted of anxiety (n=50), depression (n=40), restlessness and agitation (n=31), nightmares (n=20), insomnia (n=15) and concentration impairment (n=12). Three patients had suicidal tendency, and six patients had to be repatriated because of the effects. In more than 80 percent of the cases, the first symptoms appeared within the first 3 weeks of intake of mefloquine.
Conclusions: The neuropsychiatric effects of mefloquine are probably caused by a neurotoxic effect of the drug or, one or more of its metabolites. The frequency seems to be higher to mefloquine than to other antimalarial drugs.

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Introduction

Mefloquine is a quinoline-derivative, which is used for the treatment and prophylaxis of several forms of malaria. It is mainly used for prophylaxis against *Plasmodium falciparum*, in areas in which the parasite is resistant to chloroquine and proguanil. Mefloquine is mostly used in a weekly dose of 250 mg. The most frequently encountered adverse reactions are nausea, abdominal pain and dizziness. After therapeutic use of mefloquine, often as 1.5 g in 3 administrations, psychiatric adverse effects have been noted (1). In this paper, we report on 132 patients with neuropsychiatric effects, attributed to the intake of a prophylactic dose of mefloquine.

Patients

Since the first reports of neuropsychiatric effects in 1992 attributed to the intake of mefloquine, the Drug Safety Unit received a total of 136 of such reports. Figure 1 shows that the yearly number of reports increased concomitantly with the increasing number of exposed persons.

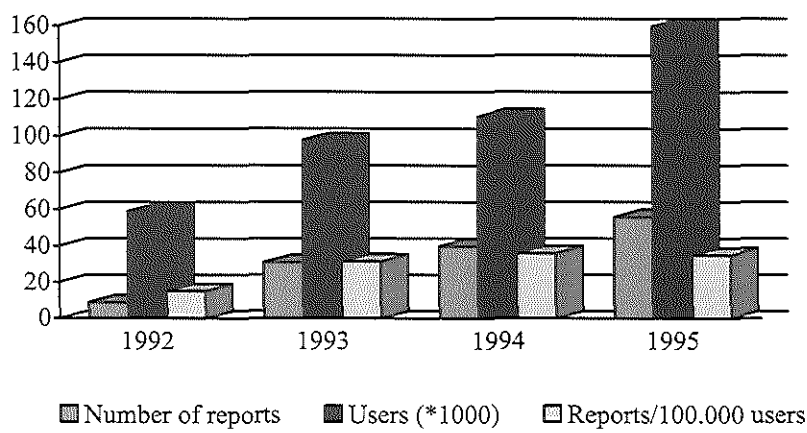

Figure 1 Number of reports of neuropsychiatric adverse reactions attributed to mefloquine

In the analysis we excluded 3 reports because we were unable to trace gender or age whereas in one report the patient had used too high a dose. The remaining

132 reports consisted of 44 males and 88 females with an average age of 37 years (median:34; range:26-71) and 35 years (median:31; range: 18-73) respectively, who had all used mefloquine as prophylaxis in a weekly dose of 250 mg. In all cases, the causal relationship between the intake of mefloquine and the appearance of neuropsychiatric reactions was considered as possible or probable according to previously defined criteria (2). The symptoms in these 132 cases are listed in table 1.

Table 1 Reported symptoms in 132 patients with neuropsychiatric reactions, attributed to the use of mefloquine

Neuropsychiatric reactions	Number of patients	Other symptoms	Number of patients
Anxiety	50	Nausea/vomiting	15
Depression	40	Palpitations	13
Agitation	31	Headache	8
Nightmares	20	Fatigue	8
Dizziness	21	Paraesthesia	7
Insomnia	15	Abdominal pain/dyspepsia	6
Concentration impairment	12	Ataxia	6
Psychosis	10	Blurred vision	5
Hallucinations	7	Hair loss	5
Depersonalisation	6	Urticaria	4
Paranoid reaction	6	Fever/shivering	3
Confusion	4	Sweating increased	3
Apathy	4	Anorexia	3
Hyperventilation	4	Tremor	2
Malaise	4	Diarroea	2
Convulsion	1	Amenorrhoea	1
		Myalgia	1
		Renal insufficiency	1

It mainly concerned anxiety, depression, agitation, concentration impairment, and insomnia. Anxiety varied from a tense feeling and nervousness to severe panic disorders. In the cases of depression, the intensity varied from feeling down to deep depression with suicidal tendency in 3 patients. Three patients had a history of depression. In 24 reports, it was explicitly stated that the patient had no previous history of psychiatric disease or symptoms; in the other reports no details regarding psychiatric history were stated. In 6 cases, disturbances were so serious that the patients were acutely repatriated. In 10 case histories, the symptoms were classified as acute psychosis. In 74 patients, discontinuation of mefloquine was followed by complete recovery without further treatment, whereas in 36 cases there were still symptoms at the moment of reporting. In the remaining 22 reports, no details were given regarding the follow-up. In 114

reports, the latent period was given between the first intake of mefloquine and the appearance of the first symptoms. In the remaining 18 reports, this was not precisely stated but also in these cases the adverse psychopathological events appeared invariably within the first 2 months of treatment. In 32 cases, the symptoms followed a fluctuating course. In these patients, the symptoms appeared one to three days after intake followed by spontaneous disappearance. After taking the next tablet, one week later, the same symptomatic pattern repeated itself. In 2 patients, symptoms disappeared after halving the weekly dose. In one patient, symptoms spontaneously disappeared despite continuation of the prophylactic intake of 250 mg mefloquine weekly. With the exception of concomitant vaccinations and use of oral contraceptives, few patients had used other drugs, which were continued without problems after recovery of the patients.

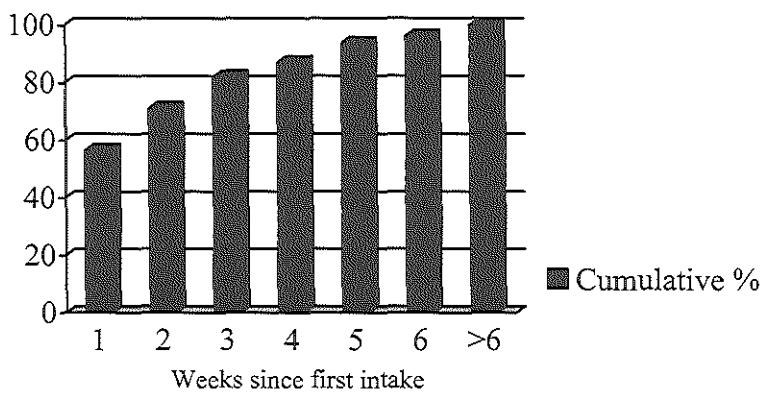

Figure 2 Psychiatric reactions to mefloquine (latent period intake-reaction in weeks)

Discussion

There can be little doubt regarding a causal relationship between the intake of mefloquine and the appearance of the neuropsychiatric adverse events in the large majority of these 132 cases. Similar cases after therapeutic as well as prophylactic treatment with mefloquine have been reported in the medical literature on several occasions (1, 3-6). The reports mainly pertained to young

individuals without a psychiatric history. Moreover, most of them had not used other drugs. The clear temporal relationship between first intake and the onset of the neuropsychiatric reaction is in strong support of a causal relationship. Although malaria itself may be accompanied by mental disturbances, this is heralded by other symptoms such as high fever. There were 3 patients with fever in our study but in none of these malaria was demonstrated. Because travelling abroad itself may cause psychological derangements, it can not be excluded that this played a causative role in some of these 132 patients. Although this may have been an important factor in the patients with a psychiatric history, it can not be excluded that the intake of mefloquine incited the reactions in these patients. It seems unlikely, however, that the mental stress of travelling solely explains the large number of reports as in the same period no reports were received regarding psychiatric symptoms to chloroquine or proguanil despite their extensive use in the Netherlands for the same indications. Also reporting bias can not explain the substantial number of reports as the possibility of neuropsychiatric effects is pointed out in the product information of both mefloquine and chloroquine, and also in the literature neuropsychiatric adverse effects and psychosis have been reported after chloroquine on several occasions (7, 8).

The mechanism of the neuropsychiatric effects to mefloquine is unclear. Like the other antimalarials with a quinoline structure, mefloquine inhibits the enzyme acetylcholinesterase (9, 10). Acetylcholine and the monoaminergic-cholinergic balance play an important role in mood disorders (11). The symptoms in the aforementioned patients, such as agitation, concentration impairment, anxiety, insomnia, and blurred vision are well-known effects of inhibitors of acetylcholinesterase such as physostigmine, carbamates and organophosphates (12). Because the inhibitory action of mefloquine on acetylcholinesterase in vitro is less than that of chloroquine and amodiaquine (10), an additional pharmacokinetic factor seems to be important. Remarkable is the fluctuating course as seen in some persons with peaking of symptoms during the first days after intake. Mefloquine has an elimination half-life of 2-3 weeks and reaches a steady state in the blood after approximately 6-11 weeks following the start of first intake of 250 mg weekly (13, 14). The latent period between the first intake and the onset of the reaction in these 132 reports is compatible with this time interval (figure 2), and could be explained by the accumulation of a

relatively high concentration of mefloquine or one or more of its metabolites at receptor sites in the central nervous system. Concomitant symptoms such as dizziness, headache, paraesthesia, blurred vision, tremor, co-ordination impairment and convulsions render support to the hypothesis that the neuropsychiatric effects have a neurotoxic pathogenesis. The fact that the pharmacokinetics of mefloquine show interindividual variability, that blood concentrations of the drug give no straightforward indication of the concentration at receptor sites in the central nervous system, and the fact that many patients already stopped the drug before presenting themselves, make it difficult to study the toxicology in these patients in more detail. In those cases in which blood levels have been assessed, these were not abnormally elevated (1).

The incidence rate of neuropsychiatric effects during prophylactic use of mefloquine is not exactly known but is probably higher than the initially estimated 1 per 13,000 treated persons (15). Although it is likely that the incidence rate of serious psychoses is lower than 1 per 10,000 treated individuals (16), the frequency of mild neuropsychiatric effects is probably much higher. Support for this hypothesis comes from a randomised clinical trial in U.S. Marines comparing 250 mg mefloquine weekly with and without loading dose, to 300 mg chloroquine weekly. In the group treated with mefloquine, insomnia and nightmares were significantly more frequent. Although also depression was more frequent in the groups on mefloquine, this tended to decrease on continued treatment (13).

In conclusion, both the literature and results from our study demonstrate that mefloquine can also cause severe psychiatric adverse effects after prophylactic use of weekly doses of 250 mg, and suggest that these reactions are fairly frequent.

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3.2

Neuropsychiatric adverse effects attributed to mefloquine - a follow-up of 327 reports from 1992-1996

Summary

Background: Mefloquine is a quinoline-derivative, which is used for the treatment and prophylaxis of malaria. Mild neuropsychiatric adverse effects such as mild depression, fatigue, insomnia and agitation can occur soon after taking the first prophylactic dose of mefloquine and may persist for weeks afterwards.
Methods: In 1996, data on 327 patients with mild and serious neuropsychiatric effects, attributed to the use of mefloquine were collected by means of a mailed questionnaire. Information on the use of drugs, alcohol, coffee, smoking, general health and medical and psychiatric history was obtained. To make an objective assessment of the presence of psychiatric effects and the severity of these effects we used the domains anxiety, depression, and insufficiency of thinking and action, sleeping disturbances and hostility from the validated Dutch Symptom Checklist-90 (SCL90).
Results: The final study population consisted of 173 persons (59 (34%) males and 114 (66%) females) with a mean age of 39 years. As compared to a normal male reference population, males scored significantly higher on the domains sleeping disturbances, insufficiency of thinking and action, depression and anxiety. Our female study population scored significantly higher on the domains sleeping disturbances, depression and anxiety than the normal female reference population. As compared to an outpatient psychiatric reference population, no differences were observed.
Conclusions: Adverse effects attributed to mefloquine occur mainly during the first three weeks of use of mefloquine and subsequently vanish or diminish. Furthermore, one of the most important results of this study is the finding that the psycho-pathological pattern of neuropsychiatric disturbances during the use of mefloquine is not different from the pattern of outpatient psychiatric patients.

Introduction

Mefloquine is a quinoline-derivative, which is used for the treatment and prophylaxis of several forms of malaria. It is mainly used against *Plasmodium falciparum* in a weekly prophylactic dose of 250 mg. The mechanism of action is still unknown but the efficacy of mefloquine as a prophylactic agent has been confirmed in large-scale studies. Serious adverse effects including agranulocytosis and severe skin disorders have been reported to mefloquine but these effects appear to be rare (1-5). Severe neuropsychiatric reactions to mefloquine appear to be more common, with an estimated frequency of 1 in 10.000 –14.000 prophylactic courses (6-7). However, these reactions mainly occurred in patients with a past history of neurological or psychiatric diseases (8). Mild neuropsychiatric adverse effects such as mild depression, fatigue, insomnia and agitation can occur soon after taking the first prophylactic dose of mefloquine and may persist for weeks afterwards (9-12). In this paper, we report on the follow-up of 327 patients with mild and serious neuropsychiatric effects, attributed to the intake of a prophylactic dose of mefloquine.

Methods

Design

Descriptive study of a case series of 327 patients with neuropsychiatric adverse effects attributed to the intake of mefloquine during the period between 1992 and 1996.

Patients

The Drug Safety Unit of the Inspectorate for Health Care in the Netherlands received a total of 327 reports of neuropsychiatric adverse effects attributed to the intake of a prophylactic dose of mefloquine, during the period 1992-1996. In 1996 we tried to trace all these patients and sent them a questionnaire through the physician who had reported the case.

Data collection

By means of a mailed questionnaire we collected information on the use of drugs, alcohol, coffee, smoking and general health. We asked for the psychiatric and medical history prior to the use of mefloquine, and general physical

complaints regarding the various body systems during the use of mefloquine. The latter complaints were scored according to severity on a scale of one to five. To make an objective assessment of the presence of the psychiatric effects of mefloquine, and the severity of these effects we used the scales on the domains anxiety, depression, and insufficiency of thinking and action, sleeping disturbances and hostility from the validated Dutch Symptom Checklist-90 (SCL90) (17). Symptoms need to be scored on a scale of one to five varying from absent (1) to present and serious (5). The scale of each domain consists of 9-16 items and the score for one domain is calculated by adding the scores on the individual items minus the number of items and then divided by the number of items that the domain consists of.

Statistics

Statistical comparisons between the study population and the reference populations were made with the Z-test and a two-sided p-value <0.05 was considered as statistically significant.

Results

In the period between 1992 and 1996, the Drug Safety Unit of the Inspectorate for Health Care received 327 reports of neuropsychiatric adverse events which were attributed to mefloquine. There were significantly more reports from women (205 (63%)) than from men (120 (37%)). For 2 (1%) persons the gender was not reported.

Out of 327, we received 202 (62%) reactions to the mailed questionnaire of which 29 were returned because the reporting physician could not retrieve the identity of the patient (anonymous report) or the patient had moved to another practice (n=23), because the patient was not able to read Dutch (n=2), or because of other reasons (n=4). Non-response did not differ between males and females, the years in which the adverse event was reported or the severity of the reported adverse events. The final study population consisted of 173 (=202-29) persons (59 (34%) male and 114 (66%) female) with a mean age of 39 years. General characteristics of the study population are shown in table 1. The main reason for travelling to an endemic area was tourism and about 87% of the population reported to be in good health before initiation of the trip.

Despite a history of epilepsy (contra indication for the use of mefloquine), one woman used mefloquine but she did not report the occurrence of convulsions during the use of this drug.

Table 1 General characteristics of the study population

	Total (n=173)		Male (n=59)		Female (n=114)	
Age (sd)	39 years	(12.3)	37 years	(10.2)	40 years	(13.2)
Reason for travelling						
Business	13	(8%)	7	(12%)	6	(5%)
Tourist	152	(88%)	47	(80%)	105	(92%)
Business and tourist	4	(2%)	2	(3%)	2	(2%)
Eduation	4	(2%)	3	(5%)	1	(1%)
General Health*						
Good	144	(87%)	55	(93%)	89	(83%)
Bad	22	(13%)	4	(7%)	18	(17%)
Epilepsy*						
Present	1	(1%)	-		1	(1%)
Absent	169	(99%)	58	(100%)	111	(99%)
Neuropsychiatric complaints prior to the use of mefloquine*						
Yes	22	(13%)	8	(15%)	14	(13%)
No	139	(87%)	47	(85%)	92	(87%)
Psychiatric disorder in family*						
Yes	18	(11%)	9	(16%)	9	(8%)
No	153	(89%)	49	(84%)	104	(92%)
Family members with epilepsy*						
Yes	7	(4%)	2	(4%)	5	(5%)
No	155	(96%)	54	(96%)	101	(95%)
Alcohol						
No	28	(14%)	1	(2%)	27	(24%)
Seldom	30	(21%)	8	(14%)	22	(25%)
< 1 unit per day	49	(28%)	22	(38%)	27	(31%)
1-5 units per day	62	(36%)	24	(41%)	38	(44%)
>5 units per day	4	(2%)	4	(7%)	-	
χ^2 (male vs female)	15.3 ($p<0.01$)					
Smoking						
Yes	67	(39%)	24	(41%)	43	(38%)
No	106	(61%)	35	(59%)	71	(62%)
Use of addictive drugs						
Yes	8	(5%)	4	(7%)	4	(4%)
No	165	(95%)	55	(93%)	110	(96%)

* Questions were not answered by all respondents

Fifty-four (31%) respondents stated that they used other drugs concomitant to mefloquine. These were mostly antibiotics, oral contraceptives and analgesics. One woman used fluvoxamine.

The majority of the study population used alcohol and men used significantly more alcohol than women (χ^2=15.3, p=0.00009). Approximately 39% of the

study population smoked and a minority (5%) also used recreational addictive drugs.

Table 2 shows the characteristics of the reported neuropsychiatric adverse events, and the use of mefloquine. Most travellers started their antimalarial prophylaxis approximately two weeks before leaving the Netherlands, 38% started three weeks before the day of departure. The mean total duration of mefloquine intake was 31.1 days (median 24 range 1-121 days). The most frequently spontaneously mentioned adverse effects were anxiety (32%), dizziness (27%), agitation (22%) and sleeplessness (21%). The adverse effects were serious in 10 (6%) respondents as they were hospitalised for treatment of the complaints. The majority of the respondents reported more than one adverse effect. Adverse events occurred mainly in the first three weeks after starting mefloquine (126 (86%) figure 1).

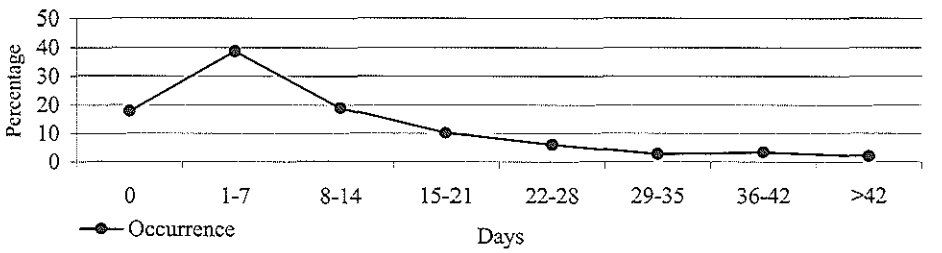

Figure 1 Occurrence of adverse effects

Of the respondents, 118 (68%) had travelled to tropical areas before the reported trip and 11% had already used mefloquine before. Among these repeated users 48% had also suffered from adverse effects during former use. Approximately 65% of the travellers recovered from the adverse effects within 28 days after cessation of use but a substantial part of the population (27%) still suffered from the reported adverse effects seven weeks after stopping prophylactic use of mefloquine (figure 2).

Table 2 Characteristics of the neuropsychiatric adverse events and the use of mefloquine

	Total	
Start mefloquine mean number of days before leaving (range)	15.9	(0-70)
Start mefloquine three weeks before leaving	59	38.1%
Mean duration of use of mefloquine in days (median, range)	31.1 (25)	(1-121)
Most frequently occurring adverse events†		
Anxiety	54	(32%)
Dizziness	45	(27%)
Agitation	37	(22%)
Sleeplessness	36	(21%)
Depression	33	(19%)
Nausea	30	(18%)
Palpitations	25	(15%)
Nightmares	24	(14%)
Lack of energy / tired	20	(12%)
Crying	20	(12%)
Nervousness	18	(11%)
Visited Physician*		
Yes, before leaving	28	(16%)
Yes, during trip	20	(12%)
Yes, after return in the Netherlands	57	(33%)
During and after the trip	16	(9%)
Contact by telephone	2	(1%)
No	48	(28%)
Hospitalisation*		
Yes	10	(6%)
No	159	(94%)
Former trips to endemic areas		
Yes	118	(68%)
No	55	(32%)
Ever used mefloquine before this time?*		
Yes	18	(11%)
No	152	(89%)
Experienced adverse effects?*		
Yes	7	(47%)
No	8	(53%)
Were there other people with adverse events?*		
Yes	64	(43%)
No	89	(57%)
Spouses with adverse events		
Yes	13	(68%)
No	6	(32%)
Did you suffer from (a) tropical disease(s)		
Yes	9	(5%)
No	158	(95%)

† Several responders mentioned more than one symptom *Questions were not answered by all respondents

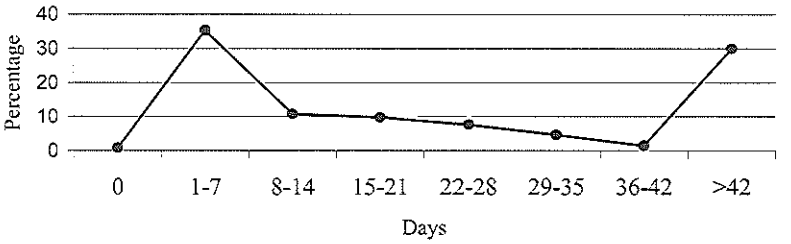

Figure 2 Duration of adverse effects

The closed questions on specific adverse effects of prophylactic use of mefloquine yielded the following risks: dizziness (66%), sleeplessness (65%), nightmares (54%), confusion (54%), nausea (42%), feeling unreal or distant (44%), sweating (49%), thought that curious things were happening to them (56%), had a bad mood (40%), 67% was feeling unhappy or sad. Females reported more nausea ($p<0.05$), feeling unhappy or sad ($p<0.1$) than men.

Apart from the self-reported adverse effects and closed questions for several adverse effects we used a part of the Dutch Symptom Checklist-90 (SCL-90) to have an objective diagnosis on the domains of anxiety, depression, insufficiency of thinking and action, sleeping disturbances and hostility at the time of mefloquine use. We compared our study population with an external normal population and an external outpatient psychiatric population. The reference populations were not different from our study population with respect to age. Table 3 shows the results of the comparison between our male and female study populations and the normal and outpatient psychiatric male reference populations. As compared to the normal reference population, our male study population scored significantly higher on the domains sleeping disturbances, insufficiency of thinking and action, depression and anxiety. The score on the domain hostility was comparable between the two populations. The scores of our study population were not different from the outpatient psychiatric reference population. Our female study population scored significantly higher on the domains sleeping disturbances, depression and anxiety as compared to the normal reference population. The scores on the domains hostility and insufficiency of thinking and action were comparable between the two populations. As for males, the scores of our female study population were not different from the outpatient psychiatric population.

Table 3 Comparison of the male study population and two reference populations

	Study population mean (se)		Normal population mean	(se)	p-value*	Psychiatric population mean (se)		p-value†
Males								
Hostility	7.5	(0.3)	7.5	(1.1)	-	11.3	(2.0)	0.0601
Sleeping disturbances	7.6	(0.5)	4.6	(1.0)	**0.0074**	7.6	(1.6)	-
Insufficiency of thinking and action	18.0	(1.1)	13.2	(1.8)	**0.0226**	21.2	(2.7)	0.2713
Depression	33.3	(2.0)	20.7	(2.2)	**<0.00006**	39.3	(3.8)	0.1615
Anxiety	22.7	(1.3)	13.0	(1.6)	**<0.00006**	24.5	(2.9)	0.5687
Females								
Hostility	8.3	(0.4)	7.6	(1.2)	0.523	11.8	(2.0)	0.0854
Sleeping disturbances	8.2	(0.4)	5.2	(1.3)	**0.0271**	8.0	(1.5)	0.8966
Insufficiency of thinking and action	18.0	(0.8)	14.1	(2.2)	0.0949	22.2	(2.8)	0.1499
Depression	37.5	(1.6)	23.8	(2.7)	**<0.0006**	44.4	(3.7)	0.0873
Anxiety	25.9	(1.1)	14.6	(2.0)	**<0.0006**	27.4	(2.9)	0.6312

*Comparison of the study population with the normal reference population

† Comparison of the study population with the outpatient psychiatric reference population

Discussion

This study is a description of the follow up of a subset of 327 patients who reported adverse events attributed to mefloquine to the Drug Safety Unit of the Inspectorate for Health Care during the period 1992-1996. This follow-up aimed to provide better insight into the adverse reactions attributed to the prophylactic use of mefloquine. Up to 1996, the Drug Safety Unit held a nation-wide voluntary reporting system for adverse events attributed to drugs. The presented frequencies should not be interpreted as risks for neuropsychiatric adverse effects among all users of mefloquine due to substantial underreporting of adverse events to a national voluntary reporting system, and the lack of information on the denominator.

One of the most important findings of this study is the fact that comparison of objectively assessed symptoms to those of an external reference population showed that males scored significantly higher on the domains sleeping disturbances, insufficiency of thinking and action, depression and anxiety than the normal reference population. In addition, females scored significantly higher on the domains sleeping disturbances, depression and anxiety than a normal

female reference population. The comparison of our male and female reference population with an outpatient psychiatric reference population showed that the neuropsychiatric disturbances during use of mefloquine are not different from the pattern of clinical symptoms and complaints observed in an outpatient psychiatric population. To our knowledge this is the first study which uses the SCL-90, an objective, validated psychiatric scale to obtain objective data on the effects of the use of mefloquine.

The majority of our study population used alcohol. The combination of mefloquine and alcohol is suspected to cause neuropsychiatric disturbances either because alcohol elevates mefloquine levels or because mefloquine interferes with alcohol metabolism (13,14).

In 1995, the Dutch guidelines have been changed as regards the prophylactic use of mefloquine. Before 1995, mefloquine was started on the day of departure. On the basis of case reports, which showed that adverse effects occur mainly during the first three weeks after starting mefloquine, the guidelines have been changed in the Netherlands and since then, it is advised to start mefloquine prophylaxis three weeks before the day of departure. This allows the physician to change the prophylactic regimen if (serious) adverse effects occur.

This study has several limitations. Due to underreporting and selective reporting, it is likely that only the more serious cases have come to our attention. Although this limits generalisability it is not likely that this has changed drug characteristics such as duration. Due to the retrospective character of this study we may have some problems with accurate recall. However, comparison of response rates showed no difference in response rates or severity of the complaints between the different years.

In conclusion, mefloquine is still the drug of choice in chloroquine resistant areas and its efficacy has been confirmed in large-scale studies. This case series described patients with mild and serious neuropsychiatric adverse effects. Most of these effects occur within the first three weeks and can be detected before departure if the renewed guidelines are followed. Objective assessment of the psychiatric complaints showed that these are apparent. Physicians who prescribe mefloquine need to inform the patients about the possible side effects and should recommend initiation of mefloquine at least three weeks before departure. In this way patients could change malariaprophylaxis before departure, such that adequate protection against malaria is not affected, due to side effects.

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Neuropsychiatric effects of antimalarials

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Neuropsychiatric effects of antimalarials

Summary

Objective: To study the neuropsychiatric adverse effects of antimalarial drugs.
Setting: Persons who visited a Travel Clinic in Rotterdam over a period of 3 months.
Design: Prospective cohort study on 394 persons taking mefloquine, 493 persons taking proguanil and 340 persons not taking antimalarial drugs who visited Africa, South America, Asia, or the Middle East.
Methods: All persons received a structured questionnaire within 14 days of their return to the Netherlands. The questionnaire consisted of questions regarding use of alcohol, smoking, general health, medical history, tropical diseases during the trip, and other medicines, and contained an extensive list of general complaints regarding all body systems at four levels of severity. A modified and validated version of the Profile of Mood States was included.
Results: In the study period, 2541 persons visited the Travel Clinic, of whom 1791 (70%) were both eligible and willing to co-operate. Of these 1791, data were obtained from 1501 (84%). Insomnia was most frequently encountered in users of mefloquine and mouth ulcers in proguanil users. After adjustment for gender, age, destination, and alcohol use, the relative risk for insomnia to mefloquine versus non-users of antimalarials was 1.6, and the excess risk was 6 per 100 users over an average period of 2 months. There were no significant differences between groups in depression, anxiety, agitation, and confusion. Stratification by gender demonstrated that insomnia was more common in women on mefloquine, but not in men. Also, women more frequently mentioned palpitations as an adverse event. After adjustment for age, destination, and alcohol use in women, the relative risks for insomnia and palpitations to mefloquine versus non-use of antimalarials were 2.4, and 22.5, respectively. When travellers were specifically asked for the adverse reactions they had experienced, anxiety, vertigo, agitation, and nightmares were significantly more frequently mentioned by mefloquine users.
Conclusion: Insomnia was more commonly encountered during use of mefloquine than proguanil or during non-use of antimalarials.

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Introduction

Mefloquine is a quinoline derivative, which is used for the treatment and prophylaxis of several forms of malaria. It is mainly used for prophylaxis against *Plasmodium falciparum*, in areas in which the parasite is resistant to chloroquine and proguanil. Mefloquine is predominantly used in a weekly dose of 250 mg. The most frequently encountered adverse reactions are nausea, abdominal pain, and dizziness. After therapeutic use of mefloquine, often as 1.5 g in three administrations, neuropsychiatric adverse effects have been noted (1). Similar cases after both therapeutic and prophylactic treatment with mefloquine have been reported in the medical literature on several occasions (2-13), but few data exist on the frequency of neuropsychiatric effects to mefloquine and other antimalarials. In this prospective cohort study, we investigated the occurrence of adverse events to antimalarials in travellers. We were especially interested in the frequency of mild neuropsychiatric adverse events to mefloquine in comparison to non-users of antimalarials.

Methods

Setting and baseline assessment

The study population consisted of persons who visited the Travel Clinic of the Harbour Hospital in Rotterdam, the Netherlands. All travellers completed an intake form regarding date of birth, gender, destination, and date of departure from and date of return to the Netherlands. The type of antimalarial drug they were prescribed was registered on this form. All persons whose anticipated return was before the end of the study period were asked for informed consent to participate in a health survey of travellers without further specification. Participants were told that they would receive a questionnaire after returning from their journey.

Study cohort

The study cohort consisted of all persons who visited the Travel Clinic in the period between 24 February and 24 May, 1994, *and* who had an anticipated date

of return to the Netherlands before the end of the study period, and who had given informed consent.

Questionnaire

A questionnaire was sent on the anticipated day of return with a request to complete it and send it back within 2 days. A reminder was sent to all non-responders 2 weeks after their return to the Netherlands.

The questionnaire consisted of questions regarding use of other medicines, alcohol and coffee intake, smoking, general health, medical history prior to cohort enrolment, tropical diseases during the journey, and an extensive list of general complaints regarding all body systems at four levels of severity (none, mild, moderate and severe) during the trip and after the return. In the questionnaire, a modified and validated version of the Profile of Mood States (POMS) was incorporated (14). The POMS consists of 32 questions designed to detect six categories of feelings: tension, vigour, fatigue, anger, depression and confusion. The questions are graded on a five-point intensity score for each question from "not at all to "extremely". At the end of the questionnaire, travellers were explicitly asked whether they had experienced adverse reactions to the antimalarial drugs they had used. Travellers were asked to complete the questionnaire at the time they were still using antimalarial treatment.

Analysis

Users of antimalarials were compared regarding the cumulative incidence of signs and symptoms, which were expressed as a relative risk (RR) with a 95% confidence interval (15). In the case of null values in one of the 2 x 2 cells, a chi-square or Fisher's exact test was used to compare proportions. Variables for which the distribution was significantly different between antimalarial drugs in the univariate analysis were included in a stratified analysis, and in a multivariate analysis with a Poisson regression model. All tests were two-sided with rejection of the null hypothesis at a P-value <0.05.

Results

In the study period, 2541 persons visited the Travel Clinic, of whom 1791 (70%) were both eligible and willing to co-operate. Of these 1791, data were obtained

from 1501 (84%), of whom 1449 persons had completely filled in the questionnaire. Of the remaining 52 persons, 4 died during the journey or before follow-up, to cardiovascular disease and malignancy. There was no significant difference between the 1501 responders and 290 non-responders concerning the type of antimalarial treatment. A random sample of 50% of these non-responders was telephoned to ask for the reason for non-response. Almost invariably, non-responders had lost the questionnaire, or had forgotten to complete it. Some of them no longer felt the need to return the questionnaire. None of them felt ill with the exception of one non-responder, who developed depression attributed to mefloquine. The remaining population consisted of 394 persons on mefloquine (27%), 493 on proguanil only (34%), and 139 on the combination of proguanil and chloroquine or chloroquine only (10%), whereas 392 persons (27%) had not used antimalarials.

Table 1 Characteristics of the study cohort (n=1227)

	Mefloquine (n=394)		Proguanil (n=493)		No antimalarial (n=340)	
Men	228	(57.9%)	251	(50.9%)	204	(60.0%)
Age	40.6	(SE 0.8)	42.9	(SE 0.9)	41.8	(SE 0.9)
BMI	24.2	(SE 0.2)	24.3	(SE 0.2)	24.8	(SE 0.2)
Women	166	(42.1%)	242	(49.1 %)	136	(40.0%)
Age	39.3	(SE 1.1)	39.7	(SE 1.0)	38.5	(SE 1.2)
BMI	22.8	(SE 0.3)	23.3	(SE 0.3)	22.7	(SE 0.3)
Reason for journey						
Business	73	(8.5%)	50	(10.1%)	127	(37.4%)
Tourist	321	(81.5%)	442	(89.9%)	213	(62.6%)
Duration of journey						
Days	24.4	(SE 0.6)	22.9	(SE 0.6)	21.5	(SE 0.9)
Destination						
Africa	51	(12.9%)	30	(6.1%)	56	(16. 5%)
Asia	290	(73.6%)	366	(74.2%)	147	(43.2%)
South America	49	(12.4%)	85	(17.2%)	94	(27.7%)
Middle East	4	(1.0%)	12	(2.4%)	43	(12.6%)
Alcohol intake						
No alcohol	58	(14.7%)	94	(19.1%)	76	(22.4%)
> 1 unit daily	149	(37.8%)	153	(31.0%)	129	(37.9%)
< 1 unit daily	183	(46.4%)	241	(48.9%)	132	(38.8%)
Not stated	4	(1.0%)	5	(1.0%)	3	(0.9%)
Smoking						
No smoking	260	(66.0%)	342	(69.4%)	226	(66.5%)
>20 daily	25	(6.3%)	30	(6.1%)	15	(4.4%)
<20 daily	105	(26.6%)	118	(23.9%)	99	(29.1%)
Not stated	4	(1.0%)	3	(1.0%)	-	
Coffee						
Cups/day	4.5	(SE 0.1)	4.6	(SE 0.1)	4.7	(SE 0.1)

In 31 individuals (2%), the history of exposure to antimalarials was unclear or unreliable. The final study cohort consisted of 1227 persons who visited Africa, South America, Asia, or the Middle East; it comprised 394 travellers on 250 mg mefloquine weekly, 493 on 200 mg proguanil daily without chloroquine, and 340 non-users of antimalarial drugs.

The majority of travellers were male, especially in the groups with a relatively high number of businessmen (table 1). The number of women in the proguanil group was significantly higher than in the other two groups. Of the 1279 persons, 27 returned earlier than anticipated. These were mostly businessmen who had finished their work earlier than expected, or persons who returned because of sick relatives. None of these persons returned because of encountered adverse events. There were no substantial differences between the groups regarding age and body mass index (BMI). A relatively high proportion of businessmen used no antimalarials. The number of users of alcohol in the mefloquine group was significantly higher than in the group which had not used antimalarials ($P = 0.01$). The number of smokers and the daily intake of coffee did not differ between the groups. The numbers of persons with concurrent illnesses was low in all groups and did not differ between groups. The use of other medicines was low in these healthy and relatively young cohort members. There were no significant differences between the groups regarding psychotropic drug use such as benzodiazepines, antidepressants, neuroleptics, or anticonvulsants. The use of β-blockers was significantly lower, however, in the mefloquine group, which is explained by the fact that mefloquine is contraindicated in users of β-blockers. Table 2 shows the adverse events, which were encountered during the journey in the three groups. Although the frequency of insomnia was higher in mefloquine users than in non-users, the relative risk was only moderately increased. The excess risk of insomnia to mefloquine was 5.7 per 100 users. Nausea and diarrhoea were more common in both the mefloquine and the proguanil groups, whereas the risk for mouth ulcers was increased only in users of proguanil. Stratification by gender demonstrated that these gastrointestinal complaints were more common in both male and female users of mefloquine and proguanil, but insomnia and palpitations were more commonly reported in women on mefloquine than in women not using antimalarials (table 2). Because alcohol was significantly more frequently used in the mefloquine group, and is associated with neuropsychiatric effects,

Table 2 Adverse events encountered during the journey. Cumulative incidence per 100 users

	Mefloquine	Proguanil	No drugs	Mefloquine vs no drugs RR (95%CI)	Proguanil vs no drugs RR (95%CI)
All travellers	*(n=394)*	*(n=493)*	*(n=340)*		
Dizziness	61 (15.5)	57 (11.6)	37 (10.9)	1.4 (0.9-2.1)	1.1 (0.7-1.6)
Insomnia	72 (18.3)	63 (12.8)	43 (12.6)	**1.4 (1.0-2.1)**	1.0 (0.7-1.5)
Agitation	27 (6.9)	24 (4.9)	22 (6.5)	1.1 (0.6-1.8)	0.8 (0.4-1.3)
Anxiety	20 (5.1)	13 (2.6)	17 (5.0)	1.0 (0.5-1.9)	0.5 (0.3-1.1)
Depression	12 (3.0)	10 (2.0)	11 (3.2)	0.9 (0.4-2.1)	0.6 (0.3-1.5)
Nightmares	18 (4.6)	8 (1.6)	8 (2.4)	1.9 (0.9-4.4)	0.7 (0.3-1.8)
Confusion	7 (1.8)	12 (2.4)	9 (2.6)	0.7 (0.3-1.8)	0.9 (0.4-2.2)
Nausea	91 (23.1)	107 (21.7)	41 (12.1)	1.9 (1.4-2.7)	**1.8 (1.3-2.5)**
Diarrhoea	206 (52.3)	292 (59.2)	114 (33.5)	1.6 (1.3-1.9)	**1.8 (1.5-2.1)**
Palpitations	12 (3.0)	13 (2.6)	5 (1.5)	2.1 (0.7-5.8)	1.8 (0.7-5.0)
Mouth ulcers	17 (4.3)	44 (8.9)	11 (3.2)	1.3 (0.6-2.8)	**2.8 (1.5-5.3)**
Men	*(n = 228)*	*(n = 251)*	*(n = 204)*		
Dizziness	27 (11.8)	15 (6.0)	15 (7.4)	1.6 (0.9-2.9)	0.8 (0.4-1.6)
Insomnia	37 (16.2)	26 (10.4)	30 (14.7)	1.1 (0.7-1.7)	0.7 (0.4-1.2)
Agitation	15 (6.6)	9 (3.6)	13 (6.4)	1.0 (0.5-2.1)	0.6 (0.3-1.3)
Anxiety	9 (3.9)	2 (0.8)	6 (2.9)	1.3 (0.5-3.7)	0.3 (0.1-1.3)
Depression	7 (3.1)	2 (0.8)	6 (2.9)	1.1 (0.4-3.1)	0.3 (0.1-1.3)
Nightmares	6 (2.6)	1 (0.4)	5 (2.5)	1.1 (0.3-3.5)	0.2 (0.1-1.4)
Confusion	3 (1.3)	3 (1.2)	4 (2.0)	0.7 (0.2-3.0)	0.6 (0.1-2.7)
Nausea	40 (17.5)	40 (15.9)	20 (9.8)	**1.8 (1.1-3.0)**	1.6 (0.9-2.7)
Diarrhoea	122 (53.5)	150 (59.8)	69 (33.8)	**1.6 (1.3-2.0)**	**1.8 (1.4-2.2)**
Palpitations	3 (1.3)	3 (1.2)	4 (2.0)	0.7 (0.2- 3.0)	0.6 (0.1-2.7)
Mouth ulcers	7 (3.1)	21 (8.4)	7 (3.4)	0.9 (0.3- 2.5)	**2.4 (1.1-5.6)**
Women	*(n = 166)*	*(n = 242)*	*(n = 136)*		
Dizziness	34 (20.5)	42 (17.4)	22 (16.2)	1.3 (0.8-2.1)	1.1 (0.7-1.7)
Insomnia	35 (21.1)	37 (15.3)	13 (9.6)	**2.2 (1.2-4.0)**	1.6 (0.9-2.9)
Agitation	12 (7.2)	15 (6.2)	9 (6.6)	1.1 (0.5-2.5)	0.9 (0.4-2.1)
Anxiety	11 (6.6)	11 (4.5)	11 (8.1)	0.8 (0.4-1.8)	0.6 (0.3-1.3)
Depression	5 (3.0)	8 (3.3)	5 (3.7)	0.8 (0.2-2.8)	0.9 (0.3-2.7)
Nightmares	12 (7.2)	7 (2.9)	3 (2.2)	3.3 (0.9-11.4)	1.3 (0.3-5.0)
Confusion	4 (2.4)	9 (3.7)	5 (3.7)	0.7 (0.2-2.4)	1.0 (0.4-3.0)
Nausea	51 (30.7)	67 (27.7)	21 (15.4)	**2.0 (1.3-3.1)**	**1.8 (1.2-2.8)**
Diarrhoea	84 (50.6)	142 (58.7)	45 (33.1)	**1.5 (1.2-2.0)**	**1.8 (1.4-2.3)**
Palpitations	9 (5.4)	10 (4.1)	1 (0.7)	**7.4 (1.0-57.0)**	5.6 (0.7-43.4)
Mouth ulcers	10 (6.0)	23 (9.5)	4 (2.9)	2.1 (0.7-6.4)	**3.2 (1.1-9.2)**

* Statistically significant differences printed in bold

stratification was performed. The risk for insomnia was increased to 3.7 (95% CI 1.6- 8.8) in non-users of alcohol but not in users (RR 1.2, 95% CI 0.8-1.7). In users, however, an increased risk for nightmares was noted of 3.7 (95% CI 1.1-12.7), which was not demonstrated in non-users (RR 1.1, 95% CI 0.3-3.7). In the Poisson regression model with adjustment for gender, age, destination, reason for journey, and alcohol use, the relative risk for insomnia to mefloquine versus non-users of antimalarials increased to 1.6 (95% CI 1.1-2.4). In women, adjustment for age, destination, and alcohol use increased the relative risks for insomnia and palpitations to mefloquine versus nonusers of antimalarials to 2.4 (95% CI 1.2-4.6), and to 22.5 (95% CI 1.7-301.4), respectively.

The analysis of the POMS test was restricted to those persons who completed the questionnaire while they were still taking antimalarial drugs. There were no significant differences between users of mefloquine and proguanil in the intensity scores for any of the items tension, vigour, fatigue, anger, or depression. In table 3, the number of suspected adverse reactions are listed as reported by the users of mefloquine and proguanil to the specific question.

Table 3 Adverse reactions to mefloquine and proguanil in travellers

	Mefloquine (n=394)	Proguanil (n=493)	Relative Risk (95% CI)
Anxiety	9	1	**11.3 (1.4-88.5)**
Insomnia	1	-	p>0.05
Palpitations	2	-	p>0.05
Depression	3	-	p>0.05
Vertigo	14	3	**5.8 (1.7-20.2)**
Agitation	4	-	**p=0.04**
Nausea	17	21	1.0 (0.5-1.9)
Somnolence	3	3	1.3 (0.3-6.2)
Nightmares	6	-	**p=0.008**
Vision Blurred	4	6	0.8 (0.2-2.9)
Rash	2	7	0.4 (0.1-1.7)
Confusion	1	1	1.3 (0.1-19.9)
Ataxia	2	-	p>0.05
Diarrhoea	7	8	1.1 (0.4-3.0)
Dyspepsia	10	14	0.9 (0.4-2.0)
Mouth ulcers	2	19	**0.1 (0.03-0.6)**
Any psychiatric ADR	17	3	**7.1 (2.1-24.0)**
Any neurological ADR	23	14	**2.1 (1.1-3.9)**
Any gastrointestinal ADR	38	65	0.7 (0.5-1.1)

Statistically significant differences printed in bold

Neuropsychiatric adverse reactions, notably anxiety, vertigo, agitation, and nightmares, were significantly more frequently mentioned by mefloquine users than by users of proguanil. Mouth ulcers were more frequently mentioned by users of proguanil.

Discussion

In this study, there were more complaints of insomnia in users of mefloquine than in users of proguanil or in travellers without antimalarial treatment. Although the difference was modest when expressed as a relative risk, our study suggests that there was an excess risk of insomnia of approximately 6 per 100 users in the average 2 months that travellers were abroad. The effect was not explained by destination or reason for journey, as adjustment for these factors did not substantially change the risk estimate. Insomnia was more frequent in women and in non-users of alcohol. In regular users of alcohol, nightmares were more frequent with use of mefloquine than during non-use of antimalarials. Although palpitations were frequently mentioned by women, the estimation of the relative risk was imprecise.

Unfortunately, the design of our study with a questionnaire did allow for assessment of cumulative incidences but not for the incidence rates of neuropsychiatric effects to antimalarials as this would have required a daily assessment with a diary which would probably have decreased the response rate. Many travellers on mefloquine mentioned neuropsychiatric adverse effects when specifically asked. The numbers of such reactions as listed in table 3 remain below the total number of the similar events in table 2, but for mefloquine the figures are closer to the total numbers in table 2 than for proguanil. This suggests that travellers might more readily recognise and report these events as adverse reactions, and attribute these effects more easily to mefloquine than to proguanil. Such a reporting bias might be explained by the product information, as the possibility of neuropsychiatric effects is pointed out in the product information of mefloquine, but not in that of proguanil. Even so, our study suggests that insomnia is more prevalent during use of mefloquine, and that use of alcohol may be influential.

Apparently, however, the size of our cohort study was too small to assess the incidence of serious psychiatric adverse effects. The incidence of psychiatric

effects during prophylactic use of mefloquine is not known exactly, but seems to be higher than the initially estimated 1 per 13 000 treated persons (16). Although it is likely that the frequency of serious psychoses is lower than 1 per 10 000 treated individuals (17), the frequency of mild neuropsychiatric effects is probably much higher. Support for this hypothesis comes from a randomised double-blind clinical trial in U.S. Marines comparing 250 mg mefloquine weekly with and without loading dose, to 300 mg chloroquine weekly. In this trial, nightmares were significantly more frequent in the group treated with a loading dose of 250 mg mefloquine daily for 3 days but there was no significant difference between groups in the incidence of insomnia (18).

The mechanism of psychiatric effects to mefloquine is unclear. Like the other antimalarials with a quinoline structure, mefloquine inhibits the enzyme acetylcholinesterase (19, 20). The symptoms in the aforementioned travellers, such as agitation, concentration impairment, anxiety, insomnia, and blurred vision, are well-known effects of inhibitors of acetylcholinesterase such as physostigmine, carbamates, and organophosphates (21). Because the inhibitory action of mefloquine on acetylcholinesterase in vitro is less than that of chloroquine and amodiaquine (19), an additional pharmacokinetic factor might be important.

Mefloquine has an elimination half-life of 2-3 weeks and reaches a steady state in the blood after approximately 6-11 weeks following the beginning of prophylactic treatment with 250 mg weekly (18, 22). The fact that 80% of neuropsychiatric adverse events seem to appear in the first 3 weeks of treatment (23) is compatible with this time interval, and could be explained by the accumulation of a relatively high concentration of mefloquine or one or more of its metabolites at receptor sites in the central nervous system. Concomitant symptoms such as dizziness, headache, paraesthesia, blurred vision, tremor, co-ordination impairment, and convulsions support to the hypothesis that the neuropsychiatric effects have a neurotoxic pathogenesis. The fact that blood concentrations of the drug give no straightforward indication of the concentration at receptor sites in the central nervous system, and the fact that many travellers had already stopped taking the drug before presenting themselves, makes it difficult to study the toxicology in these travellers in more detail. In those cases in which blood levels have been assessed, they were not abnormally elevated (1).

In conclusion, both the literature and results from our study demonstrate that mefloquine can cause insomnia after prophylactic use of weekly doses of 250 mg. It should be emphasised that despite its neuropsychiatric effects, mefloquine remains a useful antimalarial drug. Even so, the guidelines for prophylaxis in the Netherlands have recently been reconsidered because of an increase in reports of serious neuropsychiatric adverse effects (24). In these guidelines, it is advised to start mefloquine 3 weeks before departure. As 80% of the serious neuropsychiatric adverse events appear within 3 weeks, this facilitates a timely discontinuation or change of antimalarial prophylaxis. A second reason for starting treatment 3 weeks before departure is that it increases the likelihood of adequate antimalarial blood levels.

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5

Serious psychiatric events during travelling

5

Mefloquine increases the risk of serious psychiatric events during travelling – a nationwide case-control study

Summary

Background: Psychiatric events during travelling abroad account for a large percentage of medical repatriations arranged by medical assistance companies. Several risk factors have been proposed for the occurrence of these events and one of these may be the use of mefloquine. We performed a nation-wide case-control study in order to evaluate the risk of psychiatric events during the use of mefloquine relative to non-use of malariaprophylaxis.

Methods: We performed a case control study using medical records from four large alarm centres in the Netherlands. Cases were patients contacting the alarm centres because of psychiatric events. To every case we matched up to six controls by alarm centre, calendar time and continent of travel. All controls had contacted the alarm centres because of non-psychiatric medical reasons. Shortly after the anticipated day of return, cases and controls received a questionnaire with questions regarding travel characteristics, general health, weight, length, use of medicines, and malaria prophylaxis, use of alcohol and coffee intake.

Results: The study population consisted of 111 cases and 453 controls. As compared to non-use, the risk of psychiatric events during the use of mefloquine was 3.5 [95%CI: 1.4-8.7]. The association was not statistically significant in males but in females the risk was strongly increased with an OR of 47.1 [95%CI: 3.8-578.6]. Stratification for history of psychiatric diseases showed that the risk of psychiatric events during use of mefloquine in subjects without a history of psychiatric diseases was 3.8 [95%CI: 1.4-10.1], whereas the risk in subjects with a history of psychiatric diseases was 8.0 [95%CI: 1.8-35.8]. The use of proguanil was not associated with the occurrence of psychiatric symptoms.

Conclusion: The use of mefloquine is associated with the occurrence of psychiatric events among women and is more pronounced in patients with a history of psychiatric diseases.

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Introduction

Psychiatric syndromes during travelling abroad account for a large percentage of medical repatriations arranged by medical assistance companies (1). To date, several risk factors for psychiatric syndromes during travelling have been proposed. These risk factors include travel destination, travelling alone, route of transportation, time zone changes, use of malaria prophylaxis and history of psychiatric syndromes (1-3). The use of mefloquine remains a controversial risk factor for psychiatric events. The efficacy of this antimalarial is widely accepted, but its tolerability has been questioned. Although the level of perceived adverse events is high (24-90%), the incidence of psychiatric adverse events seems to be comparable to other chemoprophylactic regimens, particularly the combination of chloroquine and proguanil (4-10). Factors influencing tolerability of mefloquine are still not known, although we have previously shown that females and especially females with a low Body Mass Index (BMI) are more likely to experience adverse effects (6,9,11,12). Because of lack of uniformity in the literature on the tolerability of mefloquine, we performed a case-control study with the aim to assess the risk of psychiatric events during the use of malaria prophylaxis while travelling abroad.

Methods

Setting

This study was performed using the medical records of four large Dutch alarm centres ANWB, Elvia Assistance, SOS International and Eurocross. The alarm centres are associated with insurance companies that provide travel insurances. Every traveller seeking medical help while travelling or staying abroad should contact the alarm centre at least once to assure that the medical help abroad is reimbursed. If necessary, a team of specialised medical doctors confers with the local treating physicians on treatment and possibilities for transportation to the Netherlands. All contacts are filed and coded in a unique patient record and stored in an automated database. This study was approved by the Ethics Committee of the Erasmus Medical Centre Rotterdam, and written informed consent was obtained from all responding participants.

Source population

The source population consisted of all persons, 15 years or older, who contacted the alarm centre for any medical reason while travelling outside Europe between September 1st 1997 and June 1st 2000. We excluded all persons who did not live in the Netherlands, or did not write or speak the Dutch language.

Cases and controls

Cases were all persons who contacted the alarm centre for psychiatric disturbances during travelling. Cases were identified through the registry that contains coded information on medical complaints, coded by either ICPC code P or ICD-code 290-300. The date of first contact was defined as the index date. Up to six controls were selected at random from the source population of persons contacting the alarm centre for non-psychiatric but otherwise medical reasons at the time the case occurred and were matched to the case by alarm centre, calendar time (± 14 days) and continent of travelling.

Data collection

Data were collected by means of a self-administered questionnaire that was sent directly after the anticipated day of return to both cases and controls. A reminder was sent to all non-responders 1 month after their return to the Netherlands. Data were collected by means of closed questions regarding travel characteristics, general health, history of psychiatric diseases, weight, length, use of medicines, alcohol, and coffee intake, use and characteristics of malaria prophylaxis. We incorporated the validated Dutch Symptom Checklist (SCL-90) for validation of the psychiatric status. The SCL-90 is a self-report clinical rating scale oriented toward the symptomatic behaviour of medical and psychiatric outpatients. It contains 90 items, reflecting 8 subscales: sleeping problems, hostility, depression, somatic disturbances, feelings of distrust, agoraphobia, insufficiency of thinking and action, and anxiety. The answers are graded on a five-point scale ranging from "not at all (1)" to "extremely" (5). The total score is a composite score, which can be calculated by summing the scores of the subscales (13, 14).

Table 1 General characteristics of the study population

	Case (n=111)		Control (n=453)		Conditional OR (95% CI)
Male	36	(32.4%)	214	(47.2%)	reference
Female	75	(67.6%)	239	(52.8%)	**2.1 (1.3-3.4)**
Age (sd)	38.9	(14.9)	46.7	(18.5)	**p=0.001**
Body Mass Index (sd)	22.8	(2.9)	24.4	(4.0)	**p=0.003**
<20	16	(14.4%)	39	(8.6%)	reference
20-25	43	(38.7%)	197	(43.5%)	**0.5 (0.2-1.0)**
>25	22	(19.8%)	148	(32.7%)	**0.3 (0.1-0.7)**
Education					
Primary (vocational)	13	(11.7%)	71	(15.7%)	reference
Secondary (vocational)	43	(38.7%)	155	(34.2%)	1.5 (0.7-3.0)
College / University	29	(26.1%)	160	(35.3%)	1.0 (0.5-2.0)
Marital Status					
Unmarried / divorced	36	(32.4%)	222	(49.0%)	reference
Married/ living together	44	(39.6%)	131	(28.9%)	**1.9 (1.2-3.0)**
Widow/Widower	4	(3.6%)	32	(7.1%)	0.8 (0.3-2.5)
Travelling alone					
No	54	(48.6%)	306	(67.5%)	reference
Yes	31	(27.9%)	83	(18.3%)	**2.1 (1.2-3.6)**
Medical complaints					
No	22	(19.8%)	139	(30.7%)	reference
Yes	62	(55.9%)	240	(53.0%)	1.6 (0.9-2.7)
History of psychiatric disease					
No	28	(25.2%)	293	(64.4%)	reference
Yes	55	(49.5%)	79	(17.4%)	**7.0 (4.0-12.1)**
Use of medication					
No	31	(27.9%)	163	(36.0%)	reference
Yes	52	(46.8%)	213	(47.0%)	1.3 (0.8-2.2)
Use of alcohol					
No	22	(19.8%)	93	(20.5%)	reference
<1 unit per day	50	(45.0%)	185	(40.9%)	1.0 (0.5-2.1)
1-5 units per day	9	(8.1%)	106	(23.4%)	**0.3 (0.1-0.8)**
>5 units per day	1	(0.9%)	2	(0.4%)	2.3 (0.2-27.3)
Use of coffee					
No	15	(13.5%)	76	(16.8%)	reference
1-4 cups per day	49	(44.1%)	209	(46.1%)	1.3 (0.7-2.5)
5-9 cups per day	16	(14.4%)	84	(18.5%)	1.1 (0.5-2.4)
≥10 cups per day	1	(0.9 %)	11	(2.4%)	0.5 (0.1-4.4)
Smoking					
No	49	(44.1%)	264	(58.3%)	reference
Yes	34	(30.6%)	118	(26.0%)	1.5 (0.9-2.5)

Statistically significant differences printed in bold

Numbers do not add up to total because of missing values

Exposure assessment

Exposure to malaria prophylaxis during travel was assessed by the questionnaire. Subjects were classified as non-users of any chemoprophylaxis, users of proguanil, users of proguanil + chloroquine, mefloquine or other prophylaxis.

Analysis

Univariate comparisons between cases and controls were conducted with Students' t-tests in case of normally distributed continuous variables. Odds Ratios and 95% confidence intervals for the use of mefloquine or proguanil or other malaria prophylaxis as compared to non-use were estimated by multivariate conditional logistic regression analysis after adjustment for potential confounders such as age, gender, education level, body mass index (BMI), smoking, use of alcohol, use of medication, and history of psychiatric diseases. Missing values were incorporated in the analyses using the missing indicator method as described by Huberman (15).

We conducted three sensitivity analyses to examine whether our case and control definition was misclassified. On the basis of the total score on the SCL-90 cases were retained only if they had a clinical relevant score on the SCL-90 and controls were retained only if they had a normal score on the SCL-90 according to either of the specific cut-off values of the case. For males, we used the following cut-off points: 116, 124 and 131 and for females 130, 139 and 149 respectively, cut-off points which have been validated in a Dutch population (14).

Unconditional logistic regression analyses were performed in order to stratify for potential effect modification by history of psychiatric diseases. Interaction was studied according to the principles as described by Rothman (16, 17). Interaction is defined as a departure from additivity of effects, and interaction of factors A and B was present if $(OR_{A+B+}-OR_{A+B-}) - (OR_{A-B+}-1)>0$. Two tailed P-values less than 0.05 were considered significant. All analyses were done with SPSS 9.0 for Windows 95.

Results

From September 1st 1997 until June 1st 2000, 185 cases of psychiatric disturbances were identified, and to those cases, 1017 controls (1:5.5) were matched. A total of 800 (66.6%) questionnaires were received (116 cases and

684 controls). Non responders were significantly younger than responders (41 yrs vs 46 yrs, p<0.001), and more females responded than males (70.0% vs 67.2%, p=0.005). There was no difference in response rate between cases and controls. Five cases and 231 controls had to be excluded from the conditional logistic regression analyses because they either had no responding control or case matched to them. Therefore, the final study population consisted of 111 cases and 453 controls.

Basic characteristics of cases and controls are presented in table 1. Female gender, age, a low BMI, travelling alone and a history of psychiatric diseases, marital status and moderate alcohol intake were univariately associated with the occurrence of psychiatric events during travelling. Relative to non-use, the adjusted risk of psychiatric events during the use of malaria prophylaxis was 2.1 [95%CI: 1.1-3.8]. Table 2 shows the association for type of malaria prophylaxis.

Table 2 Association between use of malaria prophylaxis and the occurrence of psychiatric events

	Case (107)		Control (445)		Conditional OR (95%CI)	Conditional OR adjusted (95%CI)
Total						
No prophylaxis	71	(66.4%)	345	(77.5%)	reference	reference*
Proguanil	10	(9.3%)	34	(7.6%)	2.1 (0.9-5.1)	1.3 (0.5- 3.8)
Mefloquine	22	(20.6%)	41	(9.4%)	**3.2 (1.5-7.0)**	**3.5 (1.4-8.7)**
Other	4	(3.7%)	25	(5.6%)	0.9 (0.3-2.9)	0.7 (0.2-2.6)
Males						
No prophylaxis	25	(71.4%)	162	(67.8%)	reference	reference**
Proguanil	3	(8.6%)	11	(5.2%)	1.3 (0.3-5.6)	1.3 (0.2- 8.6)
Mefloquine	6	(17.1%)	24	(11.4%)	1.6 (0.5-5.4)	2.5 (0.5-12.1)
Other	1	(2.9%)	14	(6.6%)	0.7 (0.1-7.4)	0.3 (0.1- 5.8)
Females						
No prophylaxis	46	(63.9%)	183	(78.2%)	reference	reference**
Proguanil	7	(9.7%)	23	(9.8%)	1.4 (0.3-5.7)	1.2 (0.2-8.5)
Mefloquine	16	(22.2%)	17	(7.3%)	**10.0 (1.9-51.8)**	**47.1 (3.8-578.6)**
Other	3	(4.2%)	11	(4.7%)	0.9 (0.1-10.3)	1.3 (0.1-20.3)

*OR adjusted for gender, age, bmi, travelling alone and history of psychiatric diseases

**OR adjusted for age, bmi, travelling alone and history of psychiatric diseases

Regarding four cases and eight controls the status of malaria prophylaxis was unknown. As compared to non-use, the adjusted risk of psychiatric events during

the use of mefloquine was 3.5 [95%CI: 1.4-8.7]. Further adjustment for use of alcohol and marital status did not change the risk.

Because gender may be an effect modifier, stratified analyses were performed (table 2). The occurrence of psychiatric events was not significantly associated with the use of proguanil although the estimate was slightly elevated. The effect of mefloquine on the occurrence of psychiatric events was most pronounced among females (OR: 47.1 [95%CI: 3.8-578.6]), whereas the risk was not significantly elevated for males. Although BMI could be both a confounder and an effect modifier we were not able to explore the potential modifying effect because of low numbers in the strata. Since a history of psychiatric disease is a contraindication for the use of mefloquine we stratified for history of psychiatric diseases (table 3).

Table 3 Association between the occurrence of psychiatric events and use of malariaprophylaxis stratified for history of psychiatric disease (unconditional)

	Case	Control	OR (95%CI)	Adjusted OR (95%CI)*
No history of psychiatric diseases				
No prophylaxis	18	347	reference	reference
Proguanil	-	30	0 (0-2.8)	-
Mefloquine	8	53	**3.0 (1.2-7.5)**	**3.8 (1.4-10.1)**
History of psychiatric disease				
No malaria prophylaxis	36	92	reference	reference
Proguanil	8	7	**3.8 (1.1-13.6)**	4.0 (0.9-17.2)
Mefloquine	11	7	**7.0 (1.8-26.8)**	**8.0 (1.8-35.8)**

Statistically significant differences printed in bold

*adjusted for age, gender, BMI and travelling alone

Mefloquine use elevated the risk of psychiatric events both in persons with (OR: 8.0 [95%CI: 1.8-35.8]) and without a history of psychiatric disease (OR: 3.8 [95%CI: 1.4-10.1]).

We inspected the interaction between use of mefloquine, history of psychiatric disease and the occurrence of psychiatric events. The relative excess risk due to interaction (RERI) was 35.1 [95%CI: -68.7-138.9], implying that 81% of the cases of psychiatric events can be explained by the use of mefloquine in persons with a prior history of psychiatric disease (table 4).

We conducted three sensitivity analyses with respect to the case-control definition by using the total score on the SCL-90. By varying the cut off points

for the case definition, the odds ratio for psychiatric events during use of mefloquine increased from 2.0 [95%CI: 0.7-5.7] for the lowest, via 3.1 [95%CI: 1.0-10.0] for the middle to 6.1 [95%CI: 1.5-25.2] for the highest cut-off point.

Table 4 Estimation of interaction and relative excess risk due to interaction between exposure to mefloquine and history of psychiatric disease and occurrence of psychiatric events

	Cases		Controls		Adjusted OR*
Not exposed/no history of psychiatric disease	18	(25.4%)	223	(68.8%)	reference
Not exposed /history of psychiatric disease	34	(47.9%)	65	(20.1%)	4.6 (2.0-10.6)
Exposed / no history of psychiatric disease	8	(11.3%)	33	(10.2%)	4.9 (1.3-18.5)
Exposed/ history of psychiatric disease	11	(15.5%)	3	(0.9%)	43.6 (4.4-434.4)
Relative excess risk due to interaction					(43.6-4.6-4.9+1) = 35.1
					95%CI: (-68.7-138.9)
Proportion of cases attributable to the interaction of use of mefloquine and history of psychiatric disease					35.1/43.6 = 0.81

* OR adjusted for age, gender, bmi and travelling alone

Discussion

This study demonstrates that use of mefloquine increases the risk of psychiatric events during travelling. Stratification showed that mefloquine increases the risk in females but not in males. Despite the fact that mefloquine is contraindicated in persons with a history of psychiatric diseases (18), 18 patients with a history of psychiatric diseases used mefloquine as malaria prophylaxis. Among these subjects, the risk of a relapse during use of mefloquine was increased eightfold as compared to non-use.

Our study has some potential limitations. Selection bias is a potential threat to the validity of a field case control study and occurs whenever the inclusion of cases and controls is in some way associated with the exposure of interest. Selection bias may occur during the identification phase and as a result of non-response. Non response did not differ between cases and controls. Because neuropsychiatric adverse effects are incorporated in the data sheet, patients taking mefloquine may have reported more easily the occurrence of psychiatric events. It is unlikely, however, that this led to selection bias. Our cases were all persons who contacted the alarm centre for psychiatric symptoms while being abroad and it must be highly unusual that people who contact the alarm centre

because of psychiatric symptoms do not have psychiatric disturbances. On the other hand, the type of psychiatric syndrome may be misclassified because most patients did not visit a psychiatrist while being abroad. Under such circumstances a psychiatric differential diagnosis may be difficult to make. For this reason and because of low numbers, we did not stratify by type of psychiatric syndrome. By means of the SCL-90 we performed a sensitivity analysis on the cases and controls. The risk of psychiatric events associated with mefloquine was strongest in the category with the highest specificity with an odds ratio of 6.1 (95%CI: 1.5-25.2). This supports the fact that the outcome may be misclassified. Hence, application of the most stringent criteria increased rather than decreased the magnitude of the association. Since the information which was needed to calculate the SCL-90 score was collected only after a delay, our original case definition was considered as the most valid one.

Another limitation of this study might be the high percentage of questions on covariates in the questionnaire that were not completed. We decided to solve this problem by using the missing indicator method and thereby to prevent the loss of many subjects in multivariate models (15).

Some authors have suggested that physiological and psychological stress of intercontinental travel may confound the association between mefloquine and neuropsychiatric adverse events (6, 7, 19). Relocation, mode of transportation, travel destination, travelling alone and time zone changes are recognised stressors (1-3, 20, 21). Also being away from home in an unfamiliar and uncontrollable environment means that some travellers may be exposed to considerable stress at a time of maximal vulnerability (22). In this study, we tried to control for the effects of travel by matching on continent to which the cases travelled. All subjects went to destinations outside Europe and were transported through air, and encountered the same time zone changes. Furthermore, by matching on continent we reduced to some extent the confounding effects of extreme experiences, for example exposure to violent criminal activities which may differ per continent.

In conclusion, the use of mefloquine is associated with the occurrence of psychiatric events. Our study shows that besides other important risk factors like gender, BMI, age, history of psychiatric diseases and travelling alone, the use of mefloquine adds substantially to mental disturbances during travelling. These effects were mainly observed in women. Despite the fact that mefloquine is

contraindicated in persons with a history of psychiatric diseases, the majority of cases had such a history. Since persons with a positive history have a strong risk of relapse, other antimalarial drugs should be prescribed to such individuals.

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6

Early adverse effects of mefloquine

6.1

Neuropsychiatric changes and concentration impairment during the prophylactic use of mefloquine

Summary

Introduction: We performed a prospective cohort study to gain more insight into the neuropsychiatric side effects of mefloquine and into its effect on concentration among tourists travelling to endemic malaria areas. In addition, we tested whether these effects differed between males and females.

Methods: We enrolled all patients who consulted the Travel Clinic of the Havenziekenhuis & Institute for Tropical Diseases Rotterdam for mefloquine prophylaxis during the period May 1st 1999 and March 7th 2000. Each patient was followed from baseline (prior to starting mefloquine) up to three weeks after the start of mefloquine. We measured the intra-individual change in scores on the Dutch shortened Profile of Mood States (POMS) and in three domains of the Neurobehavioral Evaluation System (NES) that included sustained attention, coding speed and visuomotor accuracy between baseline and end of follow-up.

Results: The final cohort consisted of 179 subjects with a mean age of 39 years.
Females reported adverse events more frequently than males (p=0.005). Overall, we observed a small but significant increase in the score on the domain fatigue (0.74 points (95%CI: [0.18, 1.30]). The effect was exclusively present in females and not in males. First time users of mefloquine increased 2.81 points [95%CI: 0.70, 4.92] on the total score of the POMS and among those, women showed the largest increase of 4.58 points [95%CI: 0.74, 8.43]. We observed no changes in the continuous performance score during follow-up. The hand-eye-co-ordination task and coding speed improved significantly between the first and second measurement.

Conclusion: The use of mefloquine was associated with neuropsychiatric adverse effects. Women encountered neuropsychiatric effects more frequently than men did, which could be confirmed by validated psychological tests. Concentration impairment however, could neither be demonstrated in men or in women.

Introduction

In the Netherlands, mefloquine is currently the prophylactic drug of choice for travellers staying more than seven nights in areas of high risk of exposure to chloroquine-resistant falciparum malaria (1). Mefloquine is a quinoline derivative, which is used in a weekly dose of 250 mg weekly. In order to obtain adequate prophylactic blood levels and detection of early occurring adverse effects, mefloquine chemoprophylaxis is started three weeks before entering the endemic malaria area.

During the last years, case reports on CNS adverse events, and widespread media attention on CNS effects have influenced the clinical and public opinion on the use of mefloquine (2-5). Two types of CNS adverse events have been attributed to the use of mefloquine. The first is a sensation of dizziness, dysphoria and light-headedness and difficulty in concentrating which occur within 6 hours after intake and usually resolve within the following days. The second type is a more serious abrupt psychosis, occurring in the second week after start of prophylaxis (6). These neuropsychiatric effects seem to be more pronounced in women than in men (7-9).

The spontaneous reports on dizziness, dysphoria, light-headedness, and difficulty in concentrating have resulted in a relative contraindication for mefloquine in persons involved in tasks demanding fine co-ordination and spatial discrimination (air crews), in the Netherlands (1) and is incorporated in a WHO clause (10). This clause has many ramifications, not just for persons such as pilots and military personnel that are frequently at risk, but it has been interpreted by some to apply also to the traveller who wishes to drive a car, to dive, or to operate any machinery while taking mefloquine chemoprophylaxis. To our knowledge only three studies have been conducted to determine the effects of mefloquine on performance and none of them studies could substantiate a negative impact of mefloquine (8, 11, 12).

In view of the WHO clause on the one hand and the negative data regarding the effect of mefloquine on performance on the other hand, we designed a study to gain more insight into the effect of mefloquine on concentration and the occurrence of other neuropsychiatric adverse effects among tourists travelling to endemic malaria areas. Given the presumed gender differences in reported neuropsychiatric adverse effects during use of mefloquine, we tested whether

there were differences between males and females regarding concentration impairment and neuropsychiatric effects during the early use of mefloquine.

Methods

We conducted a prospective cohort study in the Travel Clinic of the Havenziekenhuis and Institute for Tropical Diseases Rotterdam, the Netherlands. The study was approved by the local Ethics Committee.

Cohort definition

Our potential study population consisted of all persons who were planning to make a trip to the tropics and who consulted the Travel Clinic for required vaccinations and mefloquine prophylaxis during the study period that started May 1st 1999 and ended March 7th 2000. Subjects were recruited on the first visit for travel advice (baseline), during which they were asked for written informed consent. Follow-up ended at a scheduled visit two or three weeks after start of the chemoprophylaxis but always prior to departure to the tropics. We included all subjects who received a prescription for mefloquine, and excluded all persons who had either one or more contraindications for mefloquine (history of epilepsy, psychosis or depression, known allergy or sensitivity to mefloquine, concurrent use of cardiovascular medication). Subsequently we excluded subjects who had used mefloquine in the preceding two months, and those who had other risk factors for concentration impairment (e.g. use of opioids, hypnotics or tranquillisers during the two weeks prior to testing, use of alcohol 4 hours prior to testing).

Outcome

Our first outcome was the occurrence of neuropsychiatric adverse events. All subjects were asked to write down all adverse events that were encountered during the first three weeks of use of mefloquine.

The second outcome measure was the intra-individual change in score on the Dutch shortened Profile of Mood States (POMS). The POMS is a validated questionnaire for the measurement of subjective mood. The POMS contains 32 questions and is designed to measure feelings in five domains: tension, depression, anger, fatigue, and vigour. The answers are graded on a five point

scale ranging from "not at all (0)" to "extremely (4)" (13). The total mood disturbance (TMD) is a composite overall score, which can be calculated by summing the raw scores across the four categories tension, anger, fatigue and depression and subtracting vigour.
The calculated total score ranges from –20 to 108, and an increase in TMD means an increase of mood disturbance.

Our third outcome was the intra-individual change in three domains of the validated Neurobehavioral Evaluation System (NES) that measured performances such as sustained attention, coding speed and visuomotor accuracy between the first and the follow-up visit. The NES is a series of computerised tests designed to provide quantitative neurobehavioral outcomes (14). For every subject, the reference score was assessed before start of therapy (baseline) and the index score after the second or third tablet of mefloquine (index).

Exposure to mefloquine
Previous exposure to mefloquine was assessed by questionnaire at baseline. The questionnaire was administered just before or after the conduct of the concentration tests. Use of mefloquine during the study period was assessed by means of a diary sheet, on which subjects were asked to fill out dose and dosing times from the start until the end of follow-up.

Covariates
Data on demographics, weight, height, education, travel destination, chronic co-morbidity and information on all risk factors that may vary over time, potentially related to the outcomes on the NES and POMS scales were collected at the start and end of follow-up. These included the use of alcohol, coffee, co-medication and illicit drugs.

Analysis
The primary comparison comprised the intra-individual change (delta) in the scores on the three NES domains, and the scores on the POMS domains between baseline (reference) and end of follow-up (index). Univariate analyses were conducted by means of paired T-tests. In order to study the association between time-independent covariates such as co-morbidity, age and gender and the change in scores we used linear regression models. In a second step we

identified through stratification whether the intra-individual effects were modified by gender, previous use of mefloquine, and the self reported neuropsychiatric adverse events. In order to study the association between time-dependent covariates such as use of coffee and medication and the change in scores, we used the general linear model for repeated measures. All tests were two sided with rejection of the null hypothesis at a P value <0.05. All analyses were done using SPSS for Windows version 9.0.

Results

We enrolled a total of 200 subjects in the cohort, of whom 179 (89.5%) completed follow-up. Reasons for loss to follow-up were: withdrawal of informed consent (n=12), cessation of mefloquine because of neuropsychiatric adverse effects (n=5), cancelling of the trip (n=3) and moved to another part of the Netherlands (n=1). Of the 21 subjects dropping out, 9 (42.9%) were female and 12 (57.1%) were males. Comparison of the scores on the POMS and the NES-tests at baseline showed that dropouts had significantly higher scores on the domains tension and depression than participants. There were no differences between participants and dropouts regarding the outcomes on the baseline NES-tests.

The final cohort thus consisted of 179 subjects with a mean age of 39 years. General characteristics of the study population are presented in table 1. No differences were observed between males and females regarding age, highest education, marital status, number of smokers and presence of medical complaints. Females had a significantly lower body mass index (BMI) than males (p=0.002). Only 9% were experiencing non-serious medical complaints at the time of enrolment. The destination of travel was predominantly Africa (67.4%) and the reason for travelling touristic (table 1). The majority of the study population planned their travel in company with others (88.8%). We observed no differences between males and females regarding the travel characteristics. In our cohort, 70 subjects (39.3%) had used mefloquine before and 21 subjects (30.4%) had encountered non-serious adverse events during previous use of mefloquine. Upon prompting by questionnaire, 58 subjects (21 males and 37 females) reported neuropsychiatric adverse events attributed to the

use of mefloquine (cumulative incidence 32.4%). Females reported adverse events more frequently than males (p=0.002).

Table 1 General characteristics of the study population

	Total (n=179)		Males (n=95)		Females (n=84)	
Average age in years (range)	39	(11-76)	40	(11-68)	37	(15-76)
BMI (kg/m^2) (range)	24.1	(15.8-35.8)	**24.9**	**(15.8-35.8)**	**23.2**	**(17.0-33.3)**
*Highest education**						
Primary/vocational education	16	(9.1%)	11	(11.8%)	5	(6.0%)
Secondary/vocational education	79	(44.9%)	43	(46.2%)	36	(43.4%)
College / university	81	(46.0%)	39	(41.9%)	42	(50.6%)
*Marital status**						
Unmarried	70	(40.2%)	39	(42.4%)	31	(37.8%)
Married / living together	100	(57.5%)	50	(54.3%)	50	(61.0%)
Divorced	4	(2.3%)	3	(3.3%)	1	(1.2%)
*Smoking**						
Yes	44	(24.7%)	24	(25.3%)	20	(24.1%)
No	134	(75.3%)	71	(74.7%)	63	(75.9%)
*Medical complaints**						
Yes	16	(9.0%)	7	(7.4%)	9	(11.0%)
No	161	(91.0%)	88	(92.6%)	73	(89.0%)
*Destination of travel**						
Africa	120	(67.4 %)	65	(68.4%)	55	(66.3%)
Asia	48	(27.0%)	25	(26.3%)	23	(27.7%)
South- America	8	(4.5%)	4	(4.2%)	4	(4.8%)
Combined	2	(1.1%)	1	(1.1%)	1	(1.2%)
*Reason for travelling**						
Business	10	(5.7%)	5	(5.4%)	5	(6.0%)
Touristic	149	(85.1%)	77	(83.7%)	72	(86.7%)
Both	16	(9.1%)	10	(10.9%)	6	(7.2%)
*Travelling alone**						
Yes	20	(11.2%)	10	(10.5%)	10	(12.0%)
No	158	(88.8%)	85	(89.5%)	73	(88.0%)

* numbers do not add up to total since some subjects did not answer all questions

BMI in females significantly lower than in males

The most frequently reported adverse events comprised sleeplessness (n=23), headache (n=15), fatigue (n=14), dizziness (n=13), abnormal dreams/nightmares (n=12), anxiety/depression/emotional lability (n=9). The risk of at least one neuropsychiatric adverse event was 44.6% for females (95%CI: 34.5%, 54.7%) and for males 22.1% (95%CI: 13.8%, 30.4%) (RR=1.41 [95%CI: 1.13, 1.75]). The risk of neuropsychiatric adverse events during first time use of mefloquine was 38.0% (95% CI: 28.8% , 47.1%) and after the first episode of use 24.3% (95%CI: 14.2%, 34.3%) (RR=1.22 [95%CI: 1.00, 1.49]).

With respect to the POMS, we observed small increases during follow up on all domains but the change was only significant at the domain fatigue and TMD for females (table 2). No changes were observed in males. Adjustment for time dependent covariates did not affect the results.

Table 2 Changes in scores on the Profile of Mood States (POMS)

	Score		Mean difference		
	t0	t1	t1-t0	[95% CI]	p-value
Total population					
Tension	1.86	1.96	0.10	[-0.31, 0.51]	0.629
Depression	0.53	0.86	0.33	[-0.02, 0.67]	0.061
Anger	1.54	1.64	0.10	[-0.48, 0.68]	0.734
Fatigue	**2.50**	**3.24**	**0.74**	**[0.18, 1.30]**	**0.010**
Vigour	11.33	11.31	-0.02	[-0.60, 0.56]	0.940
TMD	-4.90	-3.60	1.30	[-0.30, 2.89]	0.111
Males					
Tension	1.72	1.80	0.08	[-0.44, 0.61]	0.751
Depression	0.33	0.44	0.11	[-0.11, 0.34]	0.303
Anger	1.79	1.39	-0.40	[-1.13, 0.33]	0.282
Fatigue	2.08	2.48	0.40	[-0.28, 1.08]	0.246
Vigour	11.85	12.26	0.41	[-0.33, 1.16]	0.277
TMD	-5.94	-6.15	-0.21	[-1.85, 1.43]	0.800
Females					
Tension	2.02	2.14	0.12	[-0.53, 0.77]	0.717
Depression	0.76	1.33	0.57	[-0.12, 1.27]	0.106
Anger	1.26	1.93	0.67	[-0.26, 1.59]	0.155
Fatigue	**2.96**	**4.09**	**1.13**	**[0.21, 2.05]**	**0.017**
Vigour	10.74	10.22	-0.52	[-1.43, 0.40]	0.270
TMD	**-3.73**	**-0.73**	**3.00**	**[0.15, 5.85]**	**0.039**

Statistically significant differences printed in bold

TMD (Total Mood Disturbance)= tension + depression + anger + fatigue – vigour

Stratification for history of use of mefloquine showed that the TMD and the scores on the domains anger and TMD differed between first time and former users (table 3). Further inspection within these groups revealed that this difference was due to the significant increase on these domains among first time users, whereas no changes were observed among previous users of mefloquine (table 3). The effect of previous use did not appear in males. Among females who had used mefloquine previously, there were no changes in scores on the domains of the POMS. Among female first time users, statistically significant

Table 3 Comparison of the scores on the POMS between subjects with and without previous use of mefloquine

	Subjects with previous use (n=70)			Subjects without previous use (n=108)			Subjects with vs. without
	Mean difference	[95%CI]	p-value	Mean difference	[95%CI]	p-value	previous use p-value
Total							
Tension	0.17	[-0.54, 0.89]	0.634	0.06	[-0.45, 0.56]	0.828	0.787
Depression	-0.06	[-0.39, 0.28]	0.734	**0.58**	**[0.05, 1.11]**	**0.031**	0.075
Anger	-0.77	[-1.78, 0.24]	0.131	0.67	[-0.04, 1.37]	0.063	**0.028**
Fatigue	0.41	[-0.44, 1.27]	0.339	**0.96**	**[0.21, 1.71]**	**0.012**	0.349
Vigour	0.77	[-0.14, 1.68]	0.096	-0.54	[-1.30, 0.22]	0.164	0.031
TMD	-1.01	[-3.44, 1.41]	0.407	**2.81**	**[0.70, 4.92]**	**0.010**	**0.021**
Males							
Tension	0.10	[-0.93, 1.13]	0.846	0.07	[-0.47, 0.62]	0.790	0.292
Depression	0.05	[-0.18, 0.28]	0.660	0.16	[-0.19, 0.52]	0.355	0.619
Anger	-1.12	[-2.44, 0.19]	0.091	0.13	[-0.72, 0.97]	0.764	0.960
Fatigue	-0.03	[-1.16, 1.12]	0.965	0.71	[-0.15, 1.57]	0.104	0.182
Vigour	1.00	[-0.04, 2.04]	0.060	-0.02	[-1.07, 1.03]	0.972	0.094
TMD	-2.00	[-4.93, 0.93]	0.175	1.09	[-0.79, 2.97]	0.251	0.065
Females							
Tension	0.27	[-0.75, 1.28]	0.595	0.04	[-0.85, 0.92]	0.932	0.818
Depression	-0.20	[-0.94, 0.54]	0.586	1.02	[-0.0003, 2.04]	0.050	0.099
Anger	-0.30	[-1.94, 1.34]	0.712	**1.23**	**[0.08, 2.37]**	**0.036**	0.742
Fatigue	1.00	[-0.37, 2.37]	0.146	1.23	[-0.04, 2.49]	0.058	0.113
Vigour	0.47	[-1.21, 2.15]	0.574	-1.08	[-2.19, 0.04]	0.058	0.120
TMD	0.30	[-3.95, 4.55]	0.886	**4.58**	**[0.74, 8.43]**	**0.021**	0.156

Statistically significant differences printed in bold

TMD (Total Mood Disturbance)= tension + depression + anger + fatigue – vigour

increases on the domain anger as well as the TMD (4.58 95% CI: [0.74, 8.43]) were observed.

Comparison of the change in score on the POMS between subjects with and without reported adverse events showed that *within* subjects reporting neuropsychiatric adverse event the scores on the domains depression and fatigue, as well as the TMD (4.59 points [95% CI: 0.92, 8.25]) increased significantly (table 4). *Between* the two groups significant differences were observed on the domains anger, vigour as well as the TMD.

Table 4 Comparison of the scores on the POMS between subjects with and without neuropsychiatric adverse events (AE's)

	Subjects with AE's (n=58)		Subjects without AE's (n=120)		
	Mean difference [95%CI]	p-value	Mean difference [95%CI]	p-value	p-value*
Tension	0.26 [-0.64, 1.16]	0.567	0.03 [-0.41, 0.46]	0.911	0.787
Depression	**0.97 [0.16, 1.77]**	**0.019**	0.03 [-0.31, 0.36]	0.883	0.075
Anger	0.97 [-0.33, 2.26]	0.142	-0.32 [0.92, 0.29]	0.300	**0.018**
Fatigue	**1.76 [0.46, 3.06]**	**0.009**	0.26 [-0.29, 0.80]	0.350	0.349
Vigour	-0.64 [-1.67, 0.39]	0.220	0.28 [-0.44, 0.99]	0.449	**0.031**
TMD	**4.59 [0.92, 8.25]**	**0.015**	-0.28 [-1.84, 1.27]	0.719	**0.021**

Statistically significant differences printed in bold *Subjects with vs. without AE's

Table 5 shows the results of the NES. We observed no changes in the continuous performance during follow-up, neither when we stratified by gender, nor for persons with and without adverse events or previous use of mefloquine.

Table 5 Scores on the NES

	Score		Mean difference		
	t0	t1	t1-t0	[95% CI]	p-value
Total population					
Continuous performance (msec)	383.22	381.39	-1.83	[-5.75, 2.09]	0.358
Hand-eye co-ordination (log RMSE)	**2.02**	**1.80**	**-0.22**	**[-0.26, -0.17]**	**<0.001**
Coding speed (sec/dig)	**2.22**	**2.10**	**-0.11**	**[-0.15, -0.08]**	**<0.001**
Males					
Continuous performance (msec)	377.69	373.15	-4.54	[-9.94, 0.87]	0.099
Hand-eye co-ordination (log RMSE)	**1.93**	**1.73**	**-0.20**	**[-0.26, -0.14]**	**<0.001**
Coding speed (sec/digit)	**2.26**	**2.17**	**-0.09**	**[-0.14, -0.05]**	**<0.001**
Females					
Continuous performance (msec)	389.42	390.63	1.20	[-4.53, 6.94]	0.677
Hand-eye co-ordination (log RMSE)	**2.12**	**1.88**	**-0.24**	**[-0.31, -0.17]**	**<0.001**
Coding speed (sec/digit)	**2.17**	**2.03**	**-0.14**	**[-0.19, -0.09]**	**<0.001**

Statistically significant differences printed in bold

Discussion

In this study we aimed to investigate whether neuropsychiatric adverse events and concentration impairment occurred during early prophylactic use of mefloquine, and whether the effects differed between males and females, and first time and previous users of mefloquine. The most important findings were the high short-term risk of encountering adverse central nervous effects (32.4%) among the population of young and healthy travellers that used mefloquine as malaria prophylaxis during the run-in period of 3 weeks. The incidence we observed is higher than previously reported incidences of 11.2% (8), 17.4% (11), and 18.7% (15) respectively. Secondly we showed that the adverse events occurred predominantly in female first time users of mefloquine and the self reported CNS events could be confirmed by means of the validated POMS questionnaire. Our results thus lead to the conclusion that women experience adverse events of mefloquine more often than men.

A possible explanation for differences between males and females might be that females are more aware of neuropsychiatric disturbances than males, and communicate this more easily than males. Another explanation for differences between males and females might be a gender specific difference in metabolism of mefloquine. Since mefloquine has a large volume of distribution, differences in concentration of mefloquine at the receptor site might be responsible for the observed differences.

Some authors have suggested that the physiological and psychological stress of intercontinental travel may be of importance for mefloquine-associated neuropsychiatric adverse events (8, 11, 16). In this study, we tried to eliminate the effects of travel by assessing the adverse effects after the third tablet of mefloquine at the time that all subjects were still at home. Our results show that neuropsychiatric adverse events occur within three weeks after starting mefloquine and occur independently of intercontinental travel.

Although we had the power to detect a difference of 5.6 msec on the CPT we did not demonstrate an impact of mefloquine on performance / concentration. These results were independent of gender, history of use of mefloquine and adverse events. Our results, together with the three earlier published studies on concentration impairment following use of mefloquine, lead to the conclusion that the reported effects of mefloquine on performance are derived from a

general feeling of discomfort rather than concentration impairment. We, as others can therefore not find objective evidence to substantiate the WHO clause. The motivation of our study was to find this evidence since the previous studies were in special populations that may not have been generalisable. The first study compared the tests of 19 subjects with adverse events with 24 matched controls, and no significant differences were found in scores on several tests of the Neurobehavioral Evaluation System (NES) between mefloquine users who experienced adverse events and those who did not (8). The second study was a double blind, randomised cross-over study of mefloquine versus placebo within 22 male and 1 female trainee pilots attending the Swiss Civil Aviation School (11). The results and conclusion of this study were that individuals who do not have a predisposition to mefloquine associated adverse events are not significantly impaired in their neurobehavioral and performance activities. However, the results cannot be generalised easily to tourists. The third study was a randomised 2-arm, double-blind, parallel group designed study performed within 40 subjects (20 male, 20 female). All subjects were healthy volunteers, who did not plan a trip to the tropics (12). The aim of this study was to assess driving performance during the use of mefloquine as compared to placebo. In this study, mefloquine did improve co-ordinated psychomotor activities necessary for safe driving compared to placebo

Before drawing conclusions we need to emphasise some limitations that may affect the internal and external validity of our study. Firstly, we compared changes within subjects all of whom took mefloquine, although this allowed for elimination of confounding by subject characteristics, we were not able to rule out learning effects or the "placebo" effect of being treated. We could not include a placebo group for ethical considerations and neither an actively treated comparator group since the alternative chemoprophylaxis is started on the day of departure. Therefore, we may have overestimated the effect on the POMS been unable to demonstrate an effect on the coding speed and hand-eye co-ordination test that are affected highly by a learning effect between first and second measurement (14). Secondly, the external validity of our study may have been affected by the selection of our study population. The selection of the cohort is based on the prescription of mefloquine to persons planning to make a trip to a tropical area for which mefloquine is advised. The choice of chemoprophylaxis is based on the absence of contraindications for the drug and the tropical area

visited. This leads to a selection of a relatively healthy cohort formed by all first time users (with no known contraindications for the drug) and travellers who had used mefloquine before but who did not encounter serious adverse events that did not lead to cessation or refusal of the drug. Stratification for history of use showed that first time users of mefloquine increased significantly in the total score of the POMS whereas the total population as well as the former users did not show a significant increase. This shows that previous use of mefloquine should be taken into account when generalising the effects to the population that takes mefloquine for chemoprophylaxis.

In conclusion, mefloquine associated neuropsychiatric adverse effects were demonstrated during the run-in period of three weeks of the use of a prophylactic dose of 250 mg weekly. The risk of these effects is higher for women, and can be objectively assessed by means of validated psychological tests. Future studies should further explore other risk factors for neuropsychiatric adverse events, and should also focus on differences in metabolism of mefloquine between males and females. In contrast with the increase in number of reports of concentration impairment during the prophylactic use of mefloquine our results are suggestive of a general feeling of discomfort rather than concentration impairment. Concentration impairment could neither be demonstrated in men or women.

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6.2

Risk factors for neuropsychiatric adverse events and concentration impairment during the prophylactic use of mefloquine

Summary

Introduction: We performed a prospective cohort study to gain more insight into risk factors for neuropsychiatric effects of mefloquine and into its effect on concentration among tourists travelling to endemic malaria areas.
Methods: We enrolled all patients who consulted the Travel Clinic of the Havenziekenhuis & Institute for Tropical Diseases Rotterdam for mefloquine prophylaxis during the period May 1st 1999 and March 7th 2000. Each patient was followed from baseline (prior to starting mefloquine) up to three weeks after start of mefloquine. We measured the intra-individual change in scores on the Dutch shortened Profile of Mood States (POMS) and in three domains of the Neurobehavioral Evaluation System (NES) that included sustained attention, coding speed and visuomotor accuracy between the first and the follow-up visit.
Results: The final cohort consisted of 179 subjects with a mean age of 39 years.
Stratification for BMI showed that the Total Mood Disturbance in females in the lowest BMI category increased 8.42 points [95%CI: 3.33, 13.50] whereas BMI did not affect the non-risk in males. Further stratification for history of use of mefloquine strengthened showing the effect that first time female users with a BMI $\leq$ 20 kg/m^2 deteriorated 9.09 points [95%CI: 3.70, 14.49]. Analyses of the CPT showed that an increase in reaction time of 15.00 msec (ns) was observed in the lowest BMI tertile of the total population. Stratification for gender showed that women with a BMI $\leq$ 20 kg/m^2 increased significantly with 22.5 msec [95%CI: 7.80, 37.20] whereas men did not change in their reaction time. Stratification for history of use showed that first time users of mefloquine with a BMI $\leq$ 20 kg/m^2 increased 23.82 msec [95%CI: 7.84, 39.80] in their reaction time and that the increase was most pronounced in first time female users with a low BMI.
Conclusion: Risk factors for mefloquine associated neuropsychiatric adverse events and concentration impairment are female gender and low body mass index. Females encounter more adverse events than males and these effects are most pronounced in women with a BMI $\leq$ 20 kg/m^2. Since these factors may be related to serum concentration, future studies should provide information on serum concentration of mefloquine and its carboxylic acid metabolite in persons with a low BMI and especially women.

Introduction

In the Netherlands, mefloquine is currently the prophylactic drug of choice for travellers staying more than seven nights in areas of high risk of exposure to chloroquine-resistant falciparum malaria (1).

In the last years, case reports on CNS adverse events, and widespread media attention to this issue have influenced the clinical and public opinion on the use of antimalarials (2-5). To date, risk factors for neuropsychiatric adverse events attributed to mefloquine are not well characterised. In order to minimise the chance of neuropsychiatric adverse events, mefloquine is contraindicated in persons with a history of seizures or a history of psychiatric diseases (1). Another risk factor for neuropsychiatric adverse events seems to be gender. The adverse events of mefloquine seem to be more pronounced in women than in men (6-8). In a previous study, we observed that gender was a risk factor for neuropsychiatric adverse events during the early use of mefloquine, which is consistent with previous studies. Although women may communicate neuropsychiatric disturbances easier than men, an alternative explanation might be a gender-associated difference in kinetics of mefloquine. Because mefloquine has a high apparent volume of distribution, Body Mass Index (BMI) might be a risk factor related to neuropsychiatric adverse events. In order to explore whether the gender differences may be due to gender alone or might be explained by differences in BMI, we aimed to identify risk factors for neuropsychiatric adverse events and concentration impairment during the early prophylactic use of mefloquine. Also, we investigated whether BMI can modify the neuropsychiatric effects of mefloquine.

Methods

We conducted a prospective cohort study in the Travel Clinic of the Havenziekenhuis and Institute for Tropical Diseases Rotterdam, the Netherlands. The study was approved by the local Ethics Committee.

Cohort definition

Our study population consisted of all persons who were planning to make a trip to the tropics and who consulted the Travel Clinic for required vaccinations and

mefloquine prophylaxis during the study period that started May 1st 1999 and ended March 7th 2000. Each person was recruited at the first visit for travel advice (baseline), during which they were asked for written informed consent. Follow-up ended at a scheduled visit two or three weeks after start of the chemoprophylaxis but always prior to departure to the tropics. We included in the cohort all subjects who received a prescription for mefloquine, thereby excluding all persons who had either one or more contraindications for mefloquine (history of epilepsy, psychosis or depression, known allergy or sensitivity to mefloquine, concurrent use of cardiovascular medication). Subsequently we excluded subjects who had used mefloquine in the preceding two months or subjects who had other risk factors for concentration impairment (e.g. use of opioids, hypnotics or tranquillisers during the two weeks prior to testing, use of alcohol 4 hours prior to testing).

Outcome

Our first outcome measure was the intra-individual change in score of the validated Dutch shortened Profile of Mood States (POMS). The POMS is a validated questionnaire for the measurement of subjective mood. The POMS contains 32 questions and is designed to measure feelings in five subscales: tension, depression, anger, fatigue, and vigour. The POMS answers are graded on a five point scale ranging from "not at all (0)" to "extremely (4)" (9). A composite overall score for total mood disturbance (TMD) was calculated by summing the raw scores across the categories tension, anger, fatigue and depression and subtracting vigour. The calculated total score ranges from –20 to +108, and an increase in the composite score on the POMS means an increase of mood disturbance.

Our second outcome was the intra-individual change in sustained attention (Continuous Performance Test (CPT)) measured by the validated Neurobehavioral Evaluation System (NES). The NES is a series of computerised tests designed to provide quantitative neurobehavioral outcomes (10). A negative value in CPT indicates that the second measurement was completed faster than the first, whereas a positive difference indicates that the reaction time decreased. For every subject, the reference score was assessed before start of therapy (baseline) and the index score after the third tablet of mefloquine (index).

Exposure to mefloquine
Previous exposure to mefloquine was assessed by questionnaire at baseline. The questionnaire was administered just before or after the conduct of the concentration tests. Use of mefloquine during the study period was assessed by means of a diary sheet, on which patients were asked to fill out dose and dosing times from the start until the end of follow-up.

Covariates
Data on weight, height, demographics, education, travel destination, chronic co-morbidity and information on all time-dependent risk factors potentially related to the outcomes on the NES and POMS scales were collected at the start and end of follow-up. These included use of alcohol, coffee, co-medication and illicit drugs.

Analysis
The primary comparison comprised the intra-individual change (delta) in the scores on the POMS, and sustained attention between baseline (reference) and end of follow-up (index). Baseline comparisons were conducted by using Students' t-tests. Univariate analyses regarding the change within subjects were conducted by means of paired sample t-tests. Linear regression models were used to study the association between time-independent covariates such as co-morbidity, age and gender and the changes in scores. In a second step we identified through stratification whether the intra-individual effects were modified by gender, age, BMI, and previous use of mefloquine. In order to study the association between time-dependent covariates such as use of coffee and medication and the change in scores, we used the general linear model for repeated measures. All tests were two sided with rejection of the null hypothesis at a P value <0.05. All analyses were done using SPSS for Windows version 9.0.

Results

In this cohort, 200 subjects were enrolled, of whom 179 (89.5%) completed follow-up. Reasons for loss to follow up were: withdrawal of informed consent (n= 12), neuropsychiatric adverse effects (n= 5), cancelling of the trip (n= 3) and moving to another part of the Netherlands (n= 1). Of the 21 subjects dropping

out, 9 (42.9%) were female and 12 (57.1%) were males. Completers were significantly older than dropouts (39 vs 31 years, p=0.008) and had a higher BMI (24.12 vs 21.94, p=0.009). There were no differences regarding initial scores on the domains anger, vigour, fatigue and TMD, however, depression (0.53 vs 1.57, p=0.022) and tension (1.86 vs 3.19, p=0.023) differed significantly between completers and non-completers. We excluded 28 subjects because they either did not return their diary sheet and/or confirmed using three tablets of mefloquine. The final cohort thus consisted of 151 subjects, all Caucasians, with a mean age of 38.4 years (SD 12.7 yr.). General characteristics of the study population are presented in table 1. Females had a significantly lower Body Mass Index (BMI) than males (p=0.009).

Table 1 General characteristics of the study population

	Total (n=151)		Males (n=78)		Females (n=73)	
Age in years (range)	38.4	(11-76)	39.9	(11-68)	36.7	(15-59)
BMI (kg/m^2) mean (range)*	24.0	(15.8-35.8)	**24.7**	**(15.8-35.8)**	**23.2**	**(17.0-31.3)**
<20	17	(11.5%)	5	(6.6%)	12	(16.7%)
20-25	78	(52.7%)	39	(51.3%)	39	(54.2%)
>25	53	(35.8%)	32	(42.1%)	21	(29.2%)
*Highest education**						
Primary/vocational education	14	(9.4%)	10	(13.2%)	4	(5.5%)
Secondary/vocational education	64	(43.0%)	33	(43.4%)	31	(42.4%)
College / university	71	(47.6%)	33	(43.4%)	38	(52.1%)
*Marital status**						
Unmarried	59	(39.9%)	31	(41.3%)	28	(38.3%)
Married / living together	86	(58.4%)	42	(56.0%)	44	(60.3%)
Divorced	3	(2.0%)	2	(2.7%)	1	(1.4%)
Smoking						
Yes	40	(26.5%)	21	(26.9%)	19	(26.0%)
No	111	(73.5%)	57	(73.1%)	54	(74.0%)
*Medical complaints**						
Yes	13	(8.7%)	5	(6.4%)	8	(11.1%)
No	137	(91.3%)	73	(93.6%)	64	(88.9%)

* numbers do not add up tot total since some subjects did not answer all questions

BMI in females significantly lower than in males (p=0.009)

Table 2 shows the effect of BMI on the intra-individual change in scores on the POMS. Modification of the effect of mefloquine by BMI was only observed

Table 2 Relationship between BMI and POMS stratified for BMI

	Total population		Males		Females	
	Mean difference [95%CI]	p-value	Mean difference [95%CI]	p-value	Mean difference [95%CI]	p-value
Tension						
BMI ≤ 20	-0.35 [-1.57, 0.87]	0.548	0.20 [-2.02, 2.42]	0.815	-0.58 [-2.24, 1.07]	0.455
21-25	0.38 [-0.30, 1.10]	0.265	-0.26 [-1.08, 0.57]	0.536	1.03 [-0.06, 2.11]	0.062
>25	-0.17 [-0.95 0.61]	0.662	0.31 [-0.76, 1.39]	0.062	-0.90 [-2.00, 0.20]	0.103
Depression						
BMI ≤ 20	0.29 [-0.40, 0.99]	0.385	-	-	0.42 [-0.61, 1.45]	0.392
21-25	0.58 [-0.16, 1.31]	0.122	0.05 [-0.34, 0.44]	0.793	1.10 [-0.33, 2.53]	0.127
>25	0.04 [-0.34, 0.42]	0.844	0.22 [-0.24, 0.67]	0.335	-0.24 [-0.94, 0.47]	0.489
Anger						
BMI ≤ 20	1.59 [-0.59, 3.76]	0.141	0.20 [-0.36, 0.76]	0.374	2.17 [-0.99, 5.32]	0.159
21-25	-0.47 [-1.60, 0.65]	0.402	-1.38 [-2.82, 0.05]	0.058	0.44 [-1.30, 2.17]	0.615
>25	0.23 [-0.40, 0.85]	0.470	0.16 [-0.72, 1.03]	0.718	0.33 [-0.60, 1.27]	0.466
Fatigue						
BMI ≤ 20	**2.53 [0.60, 4.46]**	**0.014**	0.00 [-1.52, 0.52]	1.000	**3.58 [1.05, 6.12]**	**0.010**
21-25	**1.08 [0.15, 2.01]**	**0.024**	0.56 [-0.48, 1.62]	0.283	**1.59 [0.02, 3.16]**	**0.048**
>25	-0.09 [-0.80, 0.99]	0.833	0.75 [-0.49, 1.99]	0.226	-0.90 [-2.14, 0.33]	0.143
Vigour						
BMI ≤ 20	**-2.06 [-3.44, -0.68]**	**0.006**	-0.20 [-1.82, 1.42]	0.749	**-2.83 [-4.59, -1.08]**	**0.004**
21-25	-0.14 [-1.05, 0.77]	0.759	0.03 [-1.39, 1.34]	0.970	-0.26 [-1.52, 1.01]	0.684
>25	1.04 [-0.08 , 2.15]	0.067	0.78 [-0.39, 1.95]	0.184	1.43 [-0.89, 3.74]	0.213
TMD						
BMI ≤ 20	**6.12 [2.17, 10.07]**	**0.005**	0.60 [-2.39, 3.59]	0.607	**8.42 [3.33, 13.50]**	**0.004**
21-25	1.71 [-1.33, 4.74]	0.267	-1.00 [-3.73, 1.73]	0.462	4.41 [-1.03, 9.85]	0.109
>25	-0.85 [-3.25, 1.55]	0.481	0.66 [-2.54, 3.85]	0.678	-3.14 [-6.85, 0.56]	0.092

Statistically significant differences printed in bold

among women. Women in the lowest BMI category, decreased in vigour, and the TMD increased significantly with 8.42 [95%CI 3.33- 13.50] points. In males no association was observed between the intra-individual change in TMD and BMI. Other risk factors that may affect mood such as age and smoking were not associated with the change in TMD or the change in any of the domains.

Table 3 shows the effect modification by a history of use of mefloquine upon the change in mood due to mefloquine by BMI. No changes in mood were observed in subjects who had used mefloquine more than two months preceding current use. In first time users however, a significant increase on the domain fatigue, the TMD, and a decrease on the domain vigour were observed, but only among women. These effects were most pronounced in the lowest BMI tertile, a little smaller in the mid tertile, and not present among females in the highest BMI tertile. The TMD also showed a significant increase of 9.09 points [95%CI: 3.70, 14.49] in first time female users with a BMI below 20.

The mean difference in reaction time of the total population was -0.40 msec (table 4).

Table 4 Mean difference in continuous performance (CPT) in msec after 3 tablets of mefloquine

	Total (n=149)			Males (n=76)			Females (n= 73)		
	Mean difference	[95% CI]	p-value	Mean difference	[95% CI]	p-value	Mean difference	[95% CI]	p-value
CPT Total	-0.40	[-4.48, 3.69]	0.848	-2.53	[-8.17, 3.11]	0.375	1.82	[-74.19, 7.84]	0.548
BMI									
≤ 20	15.00	[-0.04, 30.04]	0.051	-3.00	[-49.11, 43.11]	0.865	**22.50**	**[7.80, 37.20]**	**0.006**
21-25	-1.81	[-7.25, 3.63]	0.510	-1.26	[- 8.57, 6.06]	0.730	-2.36	[-10.75, 6.03]	0.572
>25	-4.75	[-11.48, 1.99]	0.163	-6.23	[-15.60, 3.14]	0.184	-2.62	[-12.91, 7.67]	0.601

Statistically significant differences printed in bold

Although not significant, males improved in their reaction time and females decreased. Among different BMI categories, we observed no differences in baseline CPT. The increase in CPT was restricted to women with a low BMI and was 22.50 msec [95%CI: 7.80, 37.20]. Males did not change in their reaction time and there was no observable trend over BMI in neither males nor females. Stratification for previous use of mefloquine showed that reaction time was significantly increased in the lowest BMI tertile of first time users of mefloquine (21.07 msec [95%CI: 6.95, 35.20] (table 5). Although the effect was most pronounced in women with a BMI ≤20, multiple linear regression did not confirm significant interaction between gender and BMI in first time users.

Table 3 Relationship between previous use of mefloquine, BMI and POMS

	Total		Males		Females	
	With previous use	Without previous use	With previous use	Without previous use	With previous use	Without previous use
Tension						
BMI ≤ 20	0.33 [-7.26, 7.92]	-0.50 [-1.84, 0.84]	2.00 [-10.71, 14.71]	-	-	-0.36 [-2.12, 1.40]
21-25	0.19 [-0.84, 1.21]	0.52 [-0.42, 1.46]	-0.71 [-2.31, 0.88]	0.00 [-1.02, 1.02]	0.89 [-0.50, 2.27]	1.14 [-0.59, 2.88]
>25	0.36 [-1.21, 1.94]	-0.55 [-1.33, 0.23]	0.27 [-2.03, 2.56]	0.35 [-0.40, 1.10]	0.57 [-1.27, 2.41]	**-1.64 [-2.99, -0.29]**
Depression						
BMI≤ 20	-0.33 [-1.77, 1.10]	0.43 [-0.41, 1.27]	-	-	-	0.55 [-0.55, 1.64]
21-25	0.16 [-0.42, 0.74]	0.87 [-0.32, 2.06]	0.07 [-0.35, 0.49]	0.04 [-0.55, 0.63]	0.22 [-0.81, 1.25]	1.86 [-0.72, 4.43]
>25	-0.27 [-0.96, 0.41]	0.26 [-0.20, 0.71]	0.13 [-0.37, 0.64]	0.29 [-0.49, 1.08]	-1.14 [-3.24, 0.95]	0.21 [-0.25, 0.68]
Anger						
BMI ≤ 20	0.67 [-2.20, 3.54]	1.79 [-0.89, 4.47]	-	0.33 [-1.10, 1.77]	-	2.18 [-1.32, 5.68]
21-25	-1.78 [-3.74, 0.18]	0.43 [-0.89, 1.76]	-2.86 [-5.89, 0.17]	-0.56 [-2.11, 0.99]	-0.94 [-3.71, 1.82]	1.62 [-0.66, 3.90]
>25	-0.00 [-1.09, 1.09]	0.39 [-0.40, 1.17]	-0.33 [-1.88, 1.21]	0.59 [-0.46, 1.63]	0.71 [-0.67, 2.10]	0.14 [-1.19, 1.48]
Fatigue						
BMI ≤ 20	1.00 [-1.48, 3.48]	**2.86 [0.51, 5.29]**	1.00 [-11.71, 13.71]	-0.67 [-2.10, 0.77]	-	**3.82 [1.07, 6.57]**
21-25	0.90 [-0.43, 2.24]	1.20 [-0.12, 2.52]	0.07 [-1.80, 1.95]	0.84 [-0.51, 2.19]	1.56 [-0.42, 3.53]	1.62 [-0.93, 4.17]
>25	0.64 [-0.99, 3.69]	-0.29 [-1.36, 0.78]	0.93 [-1.11, 2.98]	0.59 [-1.11, 2.28]	0.00 [-3.50, 3.50]	-1.36 [-2.53, -0.19]
Vigour						
BMI ≤ 20	-0.67 [-4.46, 3.13]	**-2.36 [-3.98, -0.73]**	0.00 [-12.71, 12.71]	-0.33 [-4.13, 3.46]	-	**-2.91 [-4.84, -0.97]**
21-25	0.59 [-0.74, 1.92]	-0.65 [-1.90, 0.60]	0.36 [-1.35, 2.06]	-0.24 [-2.23, 1.75]	0.78 [-1.33, 2.89]	-1.14 [-2.71, 0.42]
>25	1.86 [-0.04, 3.69]	0.45 [-0.99, 1.90]	1.60 [-0.39, 3.59]	0.06 [-1.39, 1.51]	2.43 [-2.49, 7.35]	0.93 [-2.01, 3.87]
TMD						
BMI ≤ 20	2.33 [-1.46, 6.13]	**6.93 [2.16, 11.70]**	3.00 [-9.71, 15.71]	-1.00 [-3.48, 1.48]	-	**9.09 [3.70, 14.49]**
21-25	-1.13 [-5.55, 3.30]	3.67 [-0.49, 7.83]	-3.79 [-9.51, 1.94]	0.56 [-2.41, 3.53]	0.94 [-5.90, 7.79]	7.38 [-1.17, 15.94]
>25	-1.14 [-5.54, 3.26]	-0.65 [-3.55, 2.26]	-0.60 [-6.49, 5.29]	1.76 [-1.90, 5.43]	-2.29 [-10.66, 5.93]	-3.57 [-8.23, 1.08]

Statistically significant differences printed in bold

Discussion

In this study, two important effect modifiers for neuropsychiatric adverse events and concentration impairment were identified. The main effect modifier for neuropsychiatric adverse events as well as concentration impairment is body mass index (BMI). Subjects with a BMI ≤ 20 kg/m^2 increased significantly in TMD and reaction time, and these effects were further modified by gender. The largest effects were observed in females with a low BMI who were first time users of mefloquine.

Mefloquine is distributed extensively over tissues and the apparent volume of distribution ranges from 13-40 l/kg with a mean of 20 l/kg. It is highly protein bound (98%) and may accumulate in erythrocytes (Product information Lariam®, Roche, the Netherlands) and is predominantly excreted in the bile and faeces. Considerable pharmacokinetic differences are reported between persons of different ethnic backgrounds regarding both systemic clearance and apparent volume of distribution (11). For example, higher serum levels of mefloquine in Asians have been explained to be secondary to a relatively lower body fat content or differences in the enterohepatic circulation of mefloquine (12). However, we could not separate the effect of ethnicity and BMI since our population was entirely Caucasian. Our data suggest that adverse events occur only in subjects with a low BMI. This may be explained by the lower volume of distribution and subsequent to higher plasma levels of mefloquine. Although the mean BMI of women is lower than of men, this may solely explain the more pronounced effects in women. However, we observed a significant interaction between gender and BMI, therefore gender related differences in pharmacokinetics may also play a role, and should be investigated. Although reduction of the dose of mefloquine in subjects with a BMI ≤20 kg/m^2, and especially women with a BMI ≤20 kg/m^2, might diminish the occurrence of these effects, the effectiveness of chemoprophylaxis at lower doses should be investigated. Future studies should provide data on the relationship between dose reduction, serum levels of mefloquine, effectiveness and the occurrence of adverse events.

Before drawing conclusions on the results of our study we need to emphasise some limitations. The study population comprised persons who were planning to

Table 5 Relationship between previous use of mefloquine, BMI and CPT

	Total		Males		Females	
	With previous use	Without previous use	With previous use	Without previous use	With previous use	Without previous use
	Mean difference [95%CI]	Mean difference [95%CI]	Mean difference [95%CI]	Mean difference[95%CI]	Mean difference [95%CI]	Mean difference [95%CI]
CPT						
BMI ≤ 20	-13.33 [-109.46, 82.79]	**21.07 [6.95, 35.20]**	-24.00 [-456.01, 408.01]	11.00 [-62.15, 84.15]	-	**23.82 [7.84 , 39.80]**
21-25	- 3.94 [-13.20, 5.32]	-0.33 [-7.20, 6.55]	-0.86 [-13.96, 12.24]	-1.48 [-10.96, 8.00]	-6.33 [-20.36, 7.69]	1.05 [- 9.81, 11.91]
>25	- 0.33 [- 9.64, 8.97]	-7.83 [-17.54, 1.87]	-0.57 [-13.98, 12.84]	-11.19 [-25.22, 2.84]	0.14 [-13.65, 13.94]	- 4.00 [-19.03, 11.03]

Statistically significant differences printed in bold

make a trip and were advised to use mefloquine for prophylaxis of malaria. The follow-up measurements were conducted after intake of the third tablet of mefloquine prior to departure. Although a run-in period of three weeks allowed us to study the adverse events during the period that the subjects were still in the Netherlands thereby excluding the physiological and psychological influences from intercontinental travel. Mefloquine is the only prophylactic drug, which has a run-in period, therefore we could not use an external comparison group.

Furthermore, depletion of susceptibles (healthy user effect) might have influenced the overall results of our study, although we dealt with this by stratification for history of use of mefloquine. Stratification for history of use showed that first time users of mefloquine in the two lowest BMI tertiles did suffer from neuropsychiatric events as measured by the increase in TMD, whereas former users did not show a significant increase. Studies that do not take prior use of mefloquine into account may therefore underestimate the effect of mefloquine on the POMS and CPT.

In conclusion, mefloquine associated neuropsychiatric adverse events and concentration impairment are modified by gender and body mass index. Females encounter more adverse events than males and these effects are most pronounced in women with a BMI $\leq$ 20 kg/m^2. Since this suggests a concentration dependency of the effect, future studies should focus on the relationship between serum concentration of mefloquine and its carboxylic acid metabolite and the occurrences of neuropsychiatric adverse events.

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6.3

Neuropsychiatric adverse events are associated with increased serum levels of mefloquine

Summary

Introduction: We performed a prospective cohort study to investigate the association between serum levels of mefloquine and the occurrence of neuropsychiatric adverse events.
Methods: The study cohort comprised all patients who consulted the Travel Clinic of the Havenziekenhuis & Institute for Tropical Diseases Rotterdam for mefloquine prophylaxis during the period May 1st 1999 through March 7th 2000. Each patient was followed from baseline (prior to starting mefloquine) until three weeks after start of mefloquine. Patients who took less than 3 tablets were excluded. Serum concentrations of mefloquine and the carboxylic acid metabolite as well as the occurrence of neuropsychiatric adverse events were assessed at the end of follow-up.
Results: Our final study population consisted of 89 subjects (41 females), with a mean age of 40 years. Females had a significantly higher serum level of mefloquine than males. Stratification for BMI showed that the serum concentration of mefloquine in females with a low BMI was significantly lower than in females with a high BMI. The serum concentration of the carboxylic acid metabolite was significantly higher in subjects with a BMI ≤25 than in subjects with a BMI>25. The serum concentration of mefloquine was significantly higher in subjects with neuropsychiatric adverse events. We did not observe an association between the occurrence of neuropsychiatric adverse events and serum concentration of the carboxylic acid metabolite.
Conclusion: After intake of three tablets, serum levels of mefloquine tended to be higher in females than in males and the risk of neuropsychiatric adverse events increased with increasing serum concentrations of mefloquine.

Introduction

In the Netherlands, mefloquine is currently the prophylactic drug of choice for travellers staying more than seven nights in areas of high risk of exposure to chloroquine-resistant falciparum malaria (1). During the past years, case reports on Central Nervous System (CNS) adverse effects, and widespread media attention to this issue have influenced the clinical and public opinion regarding the use of mefloquine (2-5). The adverse effects of mefloquine seem to be more pronounced in women than in men (2, 6-8).

Mefloquine is distributed extensively in tissues and eliminated slowly, and considerable inter-individual differences in pharmacokinetic parameters have been reported (9). It is mainly excreted into bile and faeces and at steady state an average of 9% of the dose is excreted unchanged into urine, 4% as the carboxylic acid metabolite (10). It has been speculated that the parent compound (11) as well as the carboxylic acid metabolite of mefloquine may play a role in the occurrence of adverse effects (12), however, to date, no relationship between the serum levels of mefloquine as well as its main metabolite and CNS adverse effects could be shown (6). In a previous study we observed an association between the occurrence of adverse events or changes in mood and both gender and body mass index, factors that may be proxies or determinants of differences in serum levels of mefloquine or its metabolite. Despite the fact that other studies have not found an association between serum levels of mefloquine and the occurrence of adverse events, we initiated a study with the aim to investigate the relationship between serum concentrations and the occurrence of neuropsychiatric events.

Methods

We conducted a prospective cohort study in the Travel Clinic of the Havenziekenhuis and Institute for Tropical Diseases Rotterdam, the Netherlands. The study was approved by the local Ethics Committee.

Cohort definition

Our potential study population consisted of all persons who were planning to make a trip to the tropics and consulted the Travel Clinic for required vaccinations and mefloquine prophylaxis during the study period, which started

May 1st 1999 and ended March 7th 2000. Subjects were recruited during the first visit for travel advice (baseline) and follow up ended at a scheduled visit three weeks after start of the chemoprophylaxis but always prior to departure to the tropics. We included all subjects who received a prescription for mefloquine, and excluded all persons who had either one or more contraindications for mefloquine (e.g. history of epilepsy, psychosis or depression, known allergy or sensitivity to mefloquine, concurrent use of cardiovascular medication), had used mefloquine in the preceding three months, refused sampling of blood, or who did not take 3 tablets of mefloquine between baseline and follow-up.

Outcome

The outcome of the present study was the occurrence of adverse events (AE's). At the end of follow-up, subjects were asked to write down all adverse events that were encountered during the first three weeks of use of mefloquine. The occurrence of depression and fatigue was confirmed by means of the change in score on the Dutch shortened Profile of Mood States (POMS) between baseline and end of follow-up. The POMS is a standardised questionnaire for the measurement of subjective mood. The POMS contains 32 questions and is designed to measure feelings in five domains: tension, depression, anger, fatigue, and vigour. The answers are graded on a five point scale ranging from "not at all (0)" to "extremely (4)" (13). The total mood disturbance (TMD) is a composite overall score, which can be calculated by summing the raw scores across all categories and by subtracting vigour from the total score. The calculated TMD ranges from –20 to 108, and an increase in TMD means an increase of mood disturbance. For every subject, the reference score was assessed before start of therapy (baseline) and the index score after the third tablet of mefloquine (follow-up).

Determination of mefloquine

Blood samples for the measurement of the serum concentration of mefloquine and the carboxylic acid metabolite were collected at the end of follow-up. Six millilitres of blood were drawn from an antecubital vein into Vacutainers SST®. Samples were centrifuged 10 minutes (3000 rpm) within 30 minutes after collection for 10 minutes. Serum was separated and stored at -20°C until analysis.

Concentrations of mefloquine and its carboxylic acid metabolite in serum were measured by a standardised high-performance liquid chromatography (HPLC) method (14). The method employed reversed-phase chromatography on a Xterra RP 18 5µm (Waters). The mobile phase consisted of 40% acetonitrile in 50 mM sodiumphosphate buffer pH 3.1. Quantification was accomplished with 2,8-*bis*(trifluoromethyl)-4-quinolinemethanol as the internal standard. Calibration was done by calculating weighted linear regression from peak height ratios versus nominal concentration. Mefloquine and metabolite quality control serum specimens were analysed at concentrations of 50, 100, 200, 500, 1000 and 3000 ng/ml were analysed. The lower limits of quantification of mefloquine and metabolite were 50 ng/ml each.

Covariates

Data on demographics, weight, height, education, travel destination, and chronic co-morbidity were gathered at baseline. Body Mass Index (BMI) was calculated in kg/m^2. Previous exposure to mefloquine was assessed by a questionnaire that was completed during the follow-up visit. Use of mefloquine during the study period was assessed by means of a diary sheet on which subjects were asked to fill in the dose and dosing times from start until the follow-up visit.

Data analysis

Univariate analyses were conducted by means of Students' t-tests. Comparisons within subjects with and without neuropsychiatric adverse events were conducted by paired students' t-tests, and unpaired Students' t-tests were used to compare between the two groups in case of normally distributed variables and Mann-Whitney U in case of non-normally distributed variables. In order to study the relationship between day since last intake and the serum concentration of mefloquine and its carboxylic acid metabolite we used linear regression methods. In order to study the association between the occurrence of neuropsychiatric adverse events and serum levels of mefloquine, we used multiple logistic regression models with the occurrence of adverse events as dependent variable and serum levels of mefloquine as the determinant (categorised into tertiles). The potential modifying effects of gender and BMI were explored by stratification for these variables. All tests were two sided with

rejection of the null hypothesis at a P value <0.05 and conducted using SPSS for Windows version 9.0.

Results

The study population comprised 89 subjects (48 males and 41 females) with a mean age of 40 years. General characteristics of the study population and comparisons between males and females are presented in table 1. Females had a significantly lower BMI than males (p=0.024).

Table 1 General characteristics of the study population and comparisons between males and females

	Total (n=89)		Males (n=48)		Females (n=41)	
Age (years) range	39.7	18-68	41.0	21-68	38.2	18-59
BMI (kg/m^2)*	23.9	(18.3-33.0)	**24.7**	**(19.0-33.0)**	**23.1**	**(18.3-31.3)**
≤25	59	(67.0%)	28	(59.6%)	31	(75.6%)
>25	29	(33.0%)	19	(40.4%)	10	(24.4%)
Smoker						
Yes	26	(29.2%)	35	(72.9%)	28	(68.3%)
No	63	(70.8%)	13	(27.1%)	13	(31.7 %)
Medical complaints						
Yes	11	(12.4%)	3	(6.3%)	8	(19.5%)
No	78	(87.6%)	45	(93.7%)	33	(80.5%)
Use of other drugs						
Yes	21	(23.6%)	7	(14.6%)	14	(34.1%)
No	68	(76.4%)	41	(85.4%)	27	(65.9%)
Oral contraceptives					10	(24.4%)
History of use of mefloquine						
Yes	33	(37.1%)	21	(43.8%)	12	(29.3%)
No	56	(62.9%)	27	(56.3%)	29	(70.7%)

Statistically significant differences between males and females are printed in bold

* Numbers do not add up to total since not all subjects answered the question

Upon prompting by questionnaire, 25 (28%) subjects reported neuropsychiatric adverse events (AE's). The most frequently reported adverse events comprised sleeplessness and/or abnormal dreams (n=10), fatigue (n=8), headache (n=8), dizziness (n=6) and agitation/emotional lability/depression (n=5). Women (n=16) reported neuropsychiatric adverse events more frequently than men (n=9) (RR: 2.08 [95%CI: 1.03, 4.20]). By means of the POMS, we were able to validate the occurrence of fatigue and depression. Subjects reporting fatigue increased 5.75 [95%CI: 0.28, 11.22] points on this domain, whereas subjects not

reporting fatigue increased 0.64 [95%CI: -0.10, 1.39] points (p<0.001). With respect to depression, the changes were 4.25 [95%CI: -2.67, 11.17] for persons reporting depression and 0.32 [95%CI: -0.28, 0.91] for persons not reporting depression (p=0.008). Table 2 shows the changes in the separate domains of the POMS and the TMD within and between all subjects with and without neuropsychiatric adverse events. Comparisons within subjects reporting any neuropsychiatric event showed significant differences on the domains depression and fatigue.

Table 2 Comparison of the scores on the POMS between subjects with and without neuropsychiatric adverse events (AE's)

	Subjects with AE's (n=25)			Subjects without AE's (n=64)			
	Mean difference	[95%CI]	p-value*	Mean difference	[95%CI]	p-value*	p-value**
Tension	0.40	[-1.30, 2.10]	0.631	0.33	[-0.21, 0.87]	0.227	0.921
Depression	**1.68**	**[0.03, 3.33]**	**0.046**	0.11	[-0.45, 0.67]	0.698	**0.038**
Anger	1.48	[-1.29, 4.25]	0.281	0.16	[-0.63, 0.95]	0.694	0.497
Fatigue	**2.96**	**[0.61, 5.31]**	**0.016**	0.28	[-0.45, 1.01]	0.445	0.070
Vigour	0.00	[-1.49, 1.49]	1.000	0.22	[-0.87, 1.31]	0.691	0.825
TMD	6.52	[-0.73, 13.77]	0.076	0.66	[-1.48, 2.67]	0.528	0.317

*Within subject comparison **Between subject comparison -Statistically significant differences printed in bold

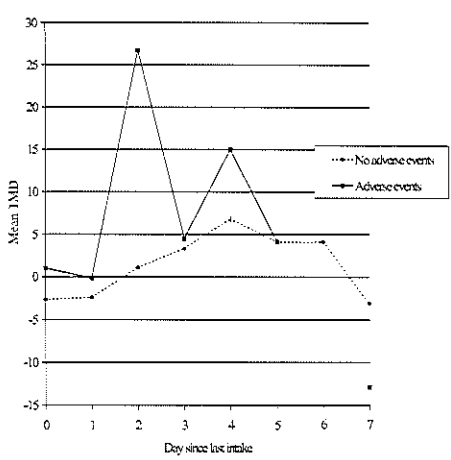

Figure 1 Change in Total Mood Disturbance (TMD) in subjects with and without neuropsychiatric adverse events.

By cohort definition, all subjects had taken 3 tablets of 250 mg mefloquine during the follow-up period. The total intake of mefloquine per kilogram body weight was 10.3. Males had a significantly lower intake of mefloquine per kilogram than females (9.5 vs 11.4, p<0.001). In figure 1, the relationship between change in TMD and day since last intake in subjects with and without neuropsychiatric adverse events is shown. Subjects reporting neuropsychiatric adverse events tended to have a larger change in TMD than subjects without

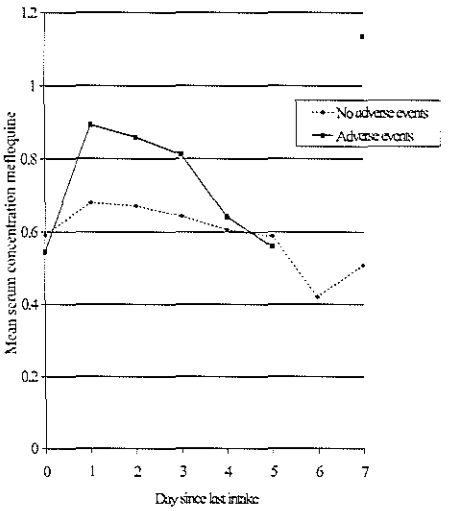

Figure 2 Relationship between day since last intake and mean serum concentration of mefloquine (µg/l) in subjects with and without neuropsychiatric adverse events.

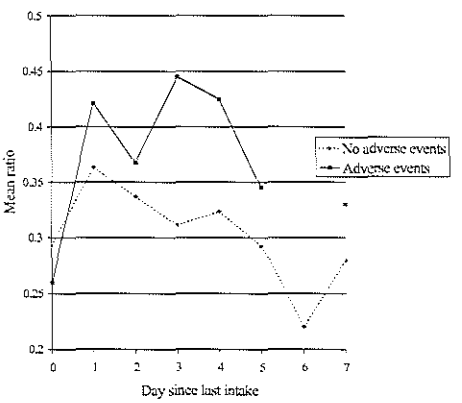

Figure 3 Relationship between day since last intake and mean ratio of (mefloquine / mefloquine + metabolite) in subjects with and without neuropsychiatric adverse events.

neuropsychiatric adverse events. In figure 2, the relationship between mean serum levels of mefloquine (µg/l) and day since last intake of mefloquine in subjects with and without neuropsychiatric adverse events is shown.
Subjects with neuropsychiatric adverse events tended to have higher serum levels of mefloquine than subjects without these adverse events.

In figure 3, the association is given between the ratio of mefloquine and the sum of mefloquine and its carboxylic acid metabolite (M/M+MMQ).
Subjects with adverse events tended to have a higher ratio than subjects without adverse events. Table 3 shows the overall and gender and BMI specific serum levels of mefloquine [M] and its carboxylic acid metabolite [MMQ] for the total study population and subjects with and without neuropsychiatric adverse events. Females had a higher mean serum level of mefloquine than males (p=0.001). There was no correlation between serum level of mefloquine and dose/kg body weight in the total population nor in males or females separately. Stratification for BMI

Table 3 Relationship serum concentrations mefloquine [M] or its metabolite [MMQ] and BMI and gender

	Total (n=89)		Subjects with adverse events (n=25)		Subjects without adverse events (n=64)		p-value*
	Mean	Range	Mean	Range	Mean	Range	
[M] µg/l							
Total	0.666	(0.315-1.508)	0.750	(0.363-1.508)	0.633	(0.315-1.177)	**p=0.029**
BMI ≤25	0.640	(0.320-1.135)	0.711	(0.397-1.135)	0.609	(0.320-1.101)	p=0.084
BMI>25	0.720	(0.315-1.508)	0.849	(0.363-1.508)	0.679	(0.315-1.177)	p=0.129
BMI ≤25 vs >25	p=0.123		p=0.265		p=0.189		
Males							
Total	0.592	(0.315-1.135)	0.716	(0.363-1.135)	0.563	(0.315-1.052)	p=0.209
BMI ≤25	0.569	(0.320-1.135)	0.762	(0.397-1.135)	0.528	(0.320-0.970)	p=0.219
BMI>25	0.621	(0.315-1.052)	0.659	(0.363-0.898)	0.612	(0.315-1.052)	p=0.671
BMI ≤25 vs >25	p=0.392		p=0.639		p=0.125		
Females							
Total	0.753	(0.373-1.508)	0.769	(0.418-1.508)	0.743	(0.373-1.177)	p=0.725
BMI ≤25	0.704	(0.374-1.101)	0.692	(0.418-1.018)	0.712	(0.373-1.001)	p=0.770
BMI >25	0.907	(0.556-1.508)	1.104	(0.873-1.508)	0.822	(0.556-1.177)	p=0.151
BMI ≤25 vs >25	**p=0.012**		**p=0.009**		p=0.234		
[MMQ] µg/l							
Total	1.351	(0.301-2.707)	1.342	(0.301-2.674)	1.354	(0.546-2.707)	p=0.912
BMI ≤25	1.471	(0.546-2.707)	1.509	(0.791-2.674)	1.458	(0.546-2.707)	p=0.720
>25	1.107	(0.301-1.985)	0.911	(0.301-1.286)	1.169	(0.638-1.985)	p=0.110
BMI≤25 vs >25	**p=0.001**		**p=0.018**		**p=0.013**		
Males							
Total	1.301	(0.584-2.315)	1.251	(0.584-2.315)	1.313	(0.706-2.086)	p=0.643
BMI ≤25	1.424	(0.790-2.315)	1.471	(0.943-2.315)	1.414	(0.791-2.086)	p=0.757
BMI>25	1.127	(0.584-1.689)	0.975	(0.584-1.286)	1.168	(0.706-1.689)	p=0.231
BMI ≤25 vs >25	**p=0.004**		p=0.152		**p=0.021**		
Females							
Total	1.409	(0.301-2.707)	1.393	(0.301-2.674)	1.419	(0.546-2.707)	p=0.894
BMI ≤25	1.519	(0.546-2.707)	1.523	(0.791-2.674)	1.515	(0.546-2.707)	p=0.970
BMI>25	1.067	(0.301-1.985)	0.826	(0.301-1.102)	1.171	(0.638-1.985)	p=0.364
BMI ≤25 vs >25	**p=0.037**		p=0.084		p=0.198		

*p value: Subjects with vs without adverse events

showed the highest serum level of mefloquine in subjects with a BMI >25 kg/m^2 and this was observed in both males and females. The serum level of the carboxylic acid metabolite was inversely correlated with BMI and we observed that females had a higher serum level of the metabolite than males.

Comparison of the serum level of mefloquine and the occurrence of adverse events showed that subjects with adverse events had significantly higher levels than subjects without adverse events (p=0.029). Stratification for BMI and gender showed, although not significant, a positive correlation with BMI and higher levels of mefloquine within each BMI category in subjects with adverse events as compared to subjects without adverse events. Except for males with adverse events with a BMI ≤25 kg/m^2 the pattern was the same over all strata. No differences were observed between subjects with and without adverse effects with respect to the serum level of the metabolite.

Table 4 Relationship between serum levels of mefloquine and the carboxylic acid metabolite (MMQ), and the occurrence of neuropsychiatric adverse events

	With events (n=25)	Without events (n=64)	Odds Ratio (95%CI)	Adjusted Odds Ratio (95%CI)*
Mefloquine				
Low (< 0.5394 µg/l)	5	26	Reference	Reference
Middle (0.5394-0.7250 µg/l)	7	23	1.58 (0.44-5.68)	1.58 (0.43-5.69)
High (> 0.7250 µg/l)	13	15	**4.51 (1.34-15.13)**	**4.83 (1.40-16.7)**
MMQ				
Low (< 1.0915 µg/l)	10	20	Reference	Reference
Middle (1.0915-1.4983 µg/l)	7	23	0.61 (0.20-1.90)	0.56 (0.18-1.82)
High (> 1.4983 µg/l)	8	21	0.76 (0.25-2.32)	0.79 (0.25-2.48)
M/M+MMQ				
Low (<0.2749)	6	23	Reference	Reference
Middle (0.2749-0.3736)	7	24	1.12 (0.33-3.83)	1.11 (0.31-3.91)
High (>0.3736)	12	17	2.71 (0.84-8.66)	2.76 (0.84-9.07)

* adjusted for age and history of use of mefloquine - Statistically significant differences printed in bold

In table 4 the association between tertiles of serum level of mefloquine, its carboxylic acid metabolite and the ratio of the metabolite and mefloquine is shown. As compared to the lowest tertile of serum level of mefloquine, the adjusted risk of neuropsychiatric adverse events in the highest tertile was 4.83 [95%CI: 1.40-16.7]. We observed a significant association between tertiles of

serum level of mefloquine and the occurrence of neuropsychiatric adverse events in both strata of BMI. In subjects with a BMI ≤25 the OR was 4.75 [95%CI: 1.11-20.39], whereas within subjects with a BMI >25 the OR was 5.00 [95%CI: 0.46-54.51]. The occurrence of neuropsychiatric adverse events was not associated with the serum concentration of the carboxylic acid metabolite or the ratio of mefloquine/mefloquine+metabolite (table 4).

Discussion

This study investigated the association between BMI or gender and serum concentrations of mefloquine and tested whether serum concentration differed between persons with and without adverse events. We showed that the risk of adverse events increased with an increasing concentration of mefloquine but not with an increasing concentration of the metabolite. Because serum levels correlate with BMI, the latter is a proxy indicator of the serum level. That is why we found that BMI was an effect modifier in our earlier studies. The observations on the relationship between serum concentrations and BMI or gender are quite interesting but difficult to explain. We observed that females have higher mefloquine serum concentrations independent of BMI. Within the highest BMI category women have higher levels of mefloquine than males, whereas the opposite effect was observed for the metabolite. Nevertheless, we found in our earlier studies that subjects with a BMI ≤25 kg/m^2 had a higher risk of neuropsychiatric adverse events. According to our findings, subjects with a low BMI can have more adverse events despite lower serum levels. This suggests that the volume of distribution is important. Mefloquine is distributed extensively over tissues and the apparent volume of distribution ranges from 13-40 l/kg with a mean of 20 l/kg. It may accumulate in erythrocytes and it is 98% protein bound (Product information Lariam®, Roche, the Netherlands). Mefloquine is predominantly excreted in the bile and faeces and considerable differences between individuals in estimates of both systemic clearance and apparent volume of distribution have been reported (15). Previously, it has been suggested that secondary to a relatively low body fat content or differences in enterohepathic circulation of mefloquine, higher drug concentrations occur in Asians as compared to Caucasians (9). In our study, we observed an association between BMI and serum levels of mefloquine and the carboxylic acid

metabolite. However, contrary to our expectations, the highest serum levels of mefloquine and the lowest serum levels of the metabolite were observed in subjects with a high BMI. One of the explanations for this might be that because of a low fat depot in subjects with a low BMI, a larger amount of mefloquine may be available for metabolism, leading to lower serum levels of mefloquine and higher serum levels of the carboxylic acid metabolite. BMI cannot explain the differences in serum levels of mefloquine that we observed between males and females. These differences may be explained by differences in fat distribution in males and females or gender specific drug metabolism, and cannot be attributed to volume of distribution alone as was done in a recently published paper (16).

In order to cause neuropsychiatric adverse events, mefloquine should pass the blood-brain barrier. A previously published paper confirmed that mefloquine, especially the (-)-enantiomere could be detected in rat-brain (17). The fact that females encounter adverse events more frequently than males might be caused by the smaller size of female brains than male brains in combination with higher blood levels of mefloquine. As brains are perfused very well, a large amount of highly fat-soluble mefloquine will pass the blood-brain-barrier and can reach the brain. Female brains may be exposed to higher levels of mefloquine, especially in the presence of higher blood levels. In males, the equilibrium between concentration in blood and brains may lead to a lower concentration at the site that is responsible for the CNS effects. Especially in females with a low BMI, (e.g. a smaller volume of distribution), a relatively large amount of mefloquine will be available to the brain, whereas in females with a larger volume of distribution, the amount of mefloquine is more equally distributed over the three compartments (blood, body fat and brains). In line with this hypothesised mechanism is the fact that no association was observed between [MMQ] and the occurrence of neuropsychiatric adverse events, since it has been shown that the metabolite could not be quantified in the brain (17).

In conclusion, our study showed an association between serum levels of mefloquine and the occurrence of neuropsychiatric adverse events. After intake of 3 tablets of mefloquine, the serum level of mefloquine tended to be higher in females than in males. As little is known about the gender-specific pharmacokinetics of mefloquine in persons with a low BMI, it may be useful to study whether a different dosing scheme in this group is justified.

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7

Atovaquone plus proguanil versus mefloquine

7

Atovaquone plus proguanil versus mefloquine for malaria prophylaxis – a focus on neuropsychiatric adverse events

Summary

Introduction: We performed a prospective, double blind, randomised study to compare the occurrence of neuropsychiatric adverse events and concentration impairment during the prophylactic use of mefloquine or atovaquone and proguanil hydrochloride (Malarone).

Methods: Our potential study population consisted of all persons who were included in the MAL30010 trial in the Travel Clinic of the Havenziekenhuis & Institute for Tropical Diseases, Rotterdam, the Netherlands. All subjects were randomised to receive either active Malarone (250 mg atovaquone plus 100 mg proguanil hydrochloride) daily plus a placebo for mefloquine weekly, or active mefloquine (250 mg) weekly plus a placebo for Malarone daily. Each subject was followed from a baseline screening visit up to the index date, 7 days after leaving the malaria endemic area. We measured the inter- and intra-individual change in mood disturbance and in three domains of the Neurobehavioral Evaluation System (NES) that included sustained attention, coding speed and visuomotor accuracy between the baseline and follow-up visit.

Results: The final cohort consisted of 119 subjects with a mean age of 35 years. Significant differences were observed between the two treatment arms. A significant deterioration in depression, anger, fatigue, vigour and Total Mood Disturbance (TMD) domains occurred during use of mefloquine but not during use of Malarone. Stratification for duration of residence in the endemic area showed that deterioration of TMD in mefloquine users was greatest in the tertile of shortest residence. In both treatment groups, sustained attention deteriorated but coding speed and visuomotor accuracy improved after travel. The change in sustained attention was greater with increased duration of stay.

Conclusion: We observed significant changes in depression, anger, fatigue, vigour and TMD only in mefloquine users, which indicates that Malarone is a safe alternative to mefloquine.

Introduction

Malaria is one of the greatest causes of morbidity and mortality in the (sub) tropical parts of the world (1), and resistance of *P. falciparum* against currently available chemoprophylaxis is increasing. Since drug resistance of *P. falciparum* is a major problem in malaria prophylaxis, and adverse events such as CNS effects of mefloquine may complicate the use of chemoprophylaxis, a new antimalarial combination of atovaquone and proguanil (Malarone) is being tested in a Phase III clinical trial (study MAL30010). The trial is conducted in order to obtain comparative information on safety and effectiveness of Malarone and mefloquine when used as a prophylactic drug in non-immune individuals travelling to areas with high risk of exposure to chloroquine-resistant falciparum malaria.

Atovaquone is a hydroxynaphtoquinone with a novel mode of anti-malarial action. In *P. falciparum* it selectively inhibits mitochondrial electron transport, diminishes pyrimidine biosynthesis and diminishes mitochondrial membrane potential, ultimately preventing cell replication (2-4). Proguanil and its main active metabolite, cycloguanil, exert their anti-malarial action through inhibition of the plasmodial dihydrofolate reductase, leading to depletion of the pyrimidine nucleotide pool, thus blocking nucleic acid synthesis and ultimately cell replication (5). A fixed-dose combination tablet containing 250 mg atovaquone and 100 mg proguanil hydrochloride is safe and effective in life-long residents of endemic areas (6). The dosage regimen is 1 tablet daily, starting 1 or 2 days before entering the malaria endemic area and continuing for 7 days after leaving the endemic area.

Mefloquine, a quinolinemethanol, is related to quinine and active as a rapid-acting blood schizontocide against all species of human malaria. It interferes with the transport of haemoglobin and other substances from the erythrocytes to the food vacuoles of the malaria parasite (7-12). The currently advised dosage regimen is one tablet of 250 mg weekly, starting three weeks before entering the malaria endemic area and continuing for four weeks after leaving this area (13). The estimated cumulative incidence of neuropsychiatric adverse events during the prophylactic use of mefloquine ranges from 11.2%-32.4% (8, 11-13). The present study is performed as a sub-study of the MAL30010 trial and was conducted to compare the occurrence of neuropsychiatric adverse events and

concentration impairment during the prophylactic use of mefloquine or Malarone.

Methods

Setting

The methods of the MAL30010 clinical trial are described in detail elsewhere (14). In summary, it is a phase III, randomised, double-blind, multi-centre, comparative study with the aim to compare the frequency and severity of adverse effects between Malarone and mefloquine chemoprophylaxis. The frequency of discontinuation because of adverse events and efficacy of chemoprophylaxis were assessed as secondary outcomes. Written informed consent was obtained from all participants and the study was approved by the Ethics Committee of the Havenziekenhuis & Institute for Tropical Diseases, Rotterdam, the Netherlands.

The study population for the MAL30010 trial comprised healthy subjects travelling to a mefloquine-indicated area. Subjects were randomised to either Malarone or mefloquine. The study consisted of an initial screening visit, a follow-up visit and two scheduled telephone contacts. Study medication was dispensed during the screening visit and all participants were instructed in the appropriate dosing regimen.

Cohort definition

Our potential study population consisted of all persons who were included in the MAL30010 trial in the Travel Clinic of the Havenziekenhuis & Institute for Tropical Diseases, Rotterdam, the Netherlands. Subjects were recruited at the initial screening visit (baseline). Follow-up ended at the index date, a scheduled visit 7 days after leaving the endemic area. We enrolled all subjects who gave consent, and excluded all persons who had risk factors for concentration impairment (e.g. use of opioids, hypnotics or tranquillisers or use of alcohol 4 hours prior to testing).

Outcome

Our neuropsychiatric outcome measures were the between and intra-individual change in score on the Dutch shortened Profile of Mood States (POMS). The

POMS is a validated questionnaire for the measurement of moods (15). The POMS contains 32 questions and is designed to measure feelings in five domains: tension, depression, anger, fatigue, and vigour. The answers are graded on a five point scale ranging from "not at all (0)" to "extremely (4)". The total mood disturbance (TMD) is a composite overall score that can be calculated by summing the raw scores across the four categories tension, anger, fatigue and depression and subtracting the score on the domain vigour. The calculated total score ranges from –20 to 108, and an increase in the composite score on the POMS means a deterioration of mood.

Our second outcome was the intra-individual change in three domains of the validated Neurobehavioral Evaluation System (NES) that measured performances such as sustained attention (response latency), coding speed and visuomotor accuracy between the first and the follow-up visit(16). The NES is a series of computerised tests designed to provide quantitative neurobehavioral outcomes.

For every subject, the reference score was assessed before start of therapy (baseline) and the index score 7 days after leaving the endemic area. The assessments were made by researchers who were unaware of the treatment allocation.

Treatment arms

All subjects were randomised to receive either Malarone or mefloquine. The dosage regimens of the drugs differ considerably. Malarone was used in a dosage of 1 tablet (250 mg atovaquone and 100 mg proguanil) daily, starting 1 to 2 days before entering the malaria-endemic area and continued until 7 days after leaving the endemic area. Mefloquine was used in a dosage of 1 tablet (250 mg) weekly, starting 3 weeks before entering the malaria endemic area and taken on the same day each week until 4 weeks after leaving the endemic area. To mask differences in dosing regimen, placebo tablets were used. All participants were randomised to receive either active Malarone (plus mefloquine placebo) or active mefloquine (plus Malarone placebo). All placebo treatment regimens were identical to the aforementioned scheme for the active ingredient of mefloquine and Malarone. Information regarding compliance with the treatment regimen was obtained by reference to the subjects' diary card and counts of returned study medication.

Covariates

Data on demographics including weight, height, date of birth, gender, race, travel destination, concurrent medications and medical conditions, and use of coffee, alcohol and illicit drugs were collected at the screening visit. At the 7-day post-travel visit, data were collected on concurrent medication and medical conditions during follow-up, and use of coffee, alcohol and illicit drugs 4 hours prior to testing.

Analysis

To be able to demonstrate a standardised difference in TMD of 0.5 with a power of 0.8 at a two-sided significance level of 0.05 would require approximately 150 persons, taking into account a participation rate of 80%.

Baseline characteristics were compared by means of student's t-tests in case of normally distributed continuous variables, and by means of χ^2 tests when comparing proportions. Our primary analysis was the comparison of the change (delta) in the scores on the separate domains of the POMS and the Total Mood Disturbance (TMD) and the three NES domains using linear regression models with the type of antimalarial as determinant. Since previous research from our group showed that body mass index (BMI) and gender may modify the effect of mefloquine on mood, we explored potential effect modification by these factors. Changes on the scores of the POMS, TMD and NES domains within both treatment arms were analysed by means of paired T-tests. All analyses were performed "as treated" and all tests were two sided with rejection of the null hypothesis at a P value <0.05. All analyses were done using SPSS for Windows version 9.0.

Results

We enrolled a total of 140 subjects in the cohort, of whom 119 (85%) completed the follow-up. Of the 21 dropouts, 14 (67%) were taking mefloquine and 7 (33%) Malarone. Reasons for dropping out were: cessation of use of the study medication because of adverse events (n=13), withdrawal of informed consent (n=4), cancelling the trip (n=1) and staying abroad (n=1). Furthermore, two subjects were excluded because they were suspected to have switched study drugs. There were no significant differences regarding reasons for dropping out

Table 1 General characteristics of the study population

	Malarone (n=61)		Mefloquine (n=58)		p-value
Gender					
Male	36	(59.0%)	38	(65.5%)	
Female	25	(41.0%)	20	(34.5%)	0.465
Average age in years (range)	35.3	(13-66)	35.1	(16-66)	0.920
BMI (kg/m^2) (range)	23.9	(17.1-33.2)	23.8	(18.3-32.3)	0.905
Highest education					
Primary/vocational education	2	(3.3%)	6	(10.3%)	0.124
Secondary/vocational education	21	(34.4%)	16	(27.6%)	0.422
College / university	38	(62.3%)	36	(62.1%)	0.945
*Marital status**					
Unmarried	14	(40.0%)	23	(40.4%)	0.180
Married / living together	34	(56.7%)	32	(56.1%)	0.208
Divorced	2	(3.3%)	2	(3.5%)	0.894
*Smoking**					
Yes	15	(25.4%)	13	(22.8%)	
No	44	(74.6%)	44	(77.2%)	0.742
Medical complaints					
Yes	3	(4.9%)	6	(10.3%)	
No	58	(95.1%)	52	(89.7%)	0.263
Previous use of mefloquine					
Yes	11	(18.3%)	17	(29.8%)	
No	49	(81.7%)	40	(70.2%)	0.145
Experienced adverse events during previous use of mefloquine					
Yes	1	(9.1%)	6	(35.3%)	
No	10	(90.9%)	11	(64.7%)	0.187**
Compliance					
Compliance to study drug (range)	97.3%	(8.7%-100%)	93.4%	(46.2%-100%)	0.076
Compliance to placebo (range)	96.4%	(33.3-100%)	96.8%	(62.5%-100%)	0.781
Destination of travel					
South Africa	15	(24.6%)	7	(12.1%)	0.079
West Africa	9	(11.5%)	7	(12.1%)	0.668
East Africa	18	(29.5%)	20	(34.5%)	0.561
Central Africa	2	(3.3%)	1	(1.7%)	1.000**
South-America	7	(11.5%)	12	(20.7%)	0.170
Other	10	(16.5%)	11	(19.0%)	0.713
Duration of stay in days (range)	18	(7-29)	19	(5-28)	0.345
Reason for travelling					
Business	-	-	2	(3.4%)	-
Touristic	60	(98.4%)	55	(94.8%)	0.356**
Both	1	(1.6%)	1	(1.7%)	-
Travelling alone					
Yes	2	(3.3%)	2	(3.4%)	
No	59	(96.7%)	56	(96.6%)	1.000**

* Numbers do not add up to total since some subjects did not answer all questions ** Fisher exact test, p-value two sided

between the two treatment arms, and the baseline POMS and NES scores were similar between completers and dropouts. However, dropouts were significantly younger than participants (p=0.004).

The final cohort thus consisted of 119 subjects with a mean age of 35 (SD 12.1) years. General characteristics of the study population are shown in table 1. We observed no differences in gender, age, BMI, highest education, marital status, number of smokers and medical complaints between the two treatment arms. Twenty-eight subjects (11 Malarone, 17 mefloquine) had previously used mefloquine. Of these, 7 (25%) had experienced non-serious adverse events at that time. The destination and mean duration of stay in the malaria endemic area were comparable between the two treatment arms (table 1).

At baseline, there were no differences between users of Malarone and mefloquine regarding the scores on the separate domains of the POMS and the Total Mood Disturbance (TMD).

Table 2 Changes in scores on the Profile of Mood States (POMS)

	Score		Mean			
	t0	t1	difference	[95% CI]	p-value*	p-value**
Malarone						
Tension	1.70	1.18	-0.52	[-1.20 , 0.16]	0.451	0.128
Depression	0.49	0.46	-0.03	[-0.54 , 0.48]	**0.006**	0.898
Anger	1.07	1.39	0.32	[-0.36 , 1.02]	0.246	0.347
Fatigue	2.49	2.75	0.26	[-0.78 , 1.30]	**0.005**	0.616
Vigour	11.82	11.54	-0.28	[-1.52 , 0.96]	**0.026**	0.655
*TMD**	-6.07	-5.75	0.32	[-2.50 , 3.13]	**0.005**	0.826
Mefloquine						
Tension	1.76	1.66	-0.10	[-0.99 , 0.79]	0.451	0.817
Depression	0.29	1.86	1.57	[0.52 , 2.62]	**0.006**	**0.004**
Anger	1.16	2.16	1.00	[0.07 , 1.93]	0.246	**0.036**
Fatigue	2.10	4.90	2.80	[1.33 , 4.26]	**0.005**	**<0.001**
Vigour	12.62	10.36	-2.26	[-3.50 , -1.01]	**0.026**	**0.001**
*TMD**	- 7.31	0.21	7.52	[3.32 , 11.71]	**0.005**	**0.001**

* p-value between treatment arms ** p-value within treatment arms

Statistically significant differences printed in bold

TMD= Tension + depression + anger+ fatigue – vigour

Comparison of the deltas (t1-t0) on the separate domains and TMD *between* the two treatment arms showed that there were significant differences between

Table 3 Relationship between residence in malaria endemic area and TMD and BMI and score on the POMS

	Number of users		Mean change in score [95%CI]		p-value between	p-value within treatment arm	
	Malarone	Mefloquine	Malarone	Mefloquine	treatment arms	Malarone	Mefloquine
TMD*							
Duration of residence							
≤16 days	30	19	-0.43 [-4.63, 3.76]	10.32 [1.94, 18.69]	**0.011**	0.834	**0.019**
17-22 days	16	23	-0.19 [-6.36, 5.99]	4.57 [0.58, 8.55]	0.163	0.949	**0.027**
>22 days	15	15	2.33 [-3.37, 8.04]	9.00 [-3.16, 21.16]	0.296	0.395	0.135
Stratification for BMI							
Tension							
BMI ≤ 25	42	39	-0.64 [-1.48, 0.19]	0.23 [-1.03, 1.49]	0.239	0.128	0.712
>25	18	19	-0.28 [-1.63, 1.07]	-0.79 [-1.73, 0.16]	0.514	0.670	0.096
Depression							
BMI ≤ 25	42	39	0.21 [-0.33, 0.75]	2.10 [0.58, 3.62]	**0.017**	0.427	**0.008**
>25	18	19	-0.56 [-1.80, 0.69]	0.47 [-0.16, 1.10]	0.123	0.359	0.132
Anger							
BMI ≤ 25	42	39	0.81 [-0.01, 1.63]	1.28 [0.19, 2.38]	0.483	0.053	**0.023**
>25	18	19	-0.83 [-2.15, 1.48]	0.42 [-1.47, 2.31]	0.264	0.198	0.645
Fatigue							
BMI ≤ 25	42	39	0.07 [-1.24, 1.38]	2.38 [0.78, 3.99]	**0.026**	0.913	**0.005**
>25	18	19	0.72 [-1.24, 2.69]	3.63 [0.39, 6.88]	0.121	0.449	**0.030**
Vigour							
BMI ≤ 25	42	39	-0.26 [-1.59, 1.07]	-1.92 [-3.50, -0.35]	0.106	0.693	**0.011**
>25	18	19	-0.33 [-3.44, 2.77]	-2.95 [-5.13, -0.77]	0.152	0.823	**0.018**
TMD*							
BMI ≤ 25	42	39	0.71 [-2.68, 4.11]	7.92 [2.10, 13.75]	**0.031**	0.673	**0.009**
>25	18	19	-0.61 [-6.45, 5.23]	6.68 [1.36, 12.00]	0.060	0.828	**0.017**

Statistically significant differences printed in bold *TMD= Tension + depression + anger + fatigue – vigour

mefloquine and Malarone with respect to depression, fatigue, vigour and TMD. The deterioration on these domains was significant only during use of mefloquine and not during use of Malarone (table 2). Stratification for gender showed that the between-treatment differences were restricted to females and were not significant in males. *Within* Malarone users, no intra-individual changes in scores on the separate domains of the POMS or the TMD were observed, and this was similar for men and women. However, *within* mefloquine users, we observed significant deterioration on the domains depression, anger, fatigue and vigour. The TMD increased with 7.52 [3.32, 11.71] points (table 2). *Within* users of mefloquine, there was no effect modification by gender.

Because the occurrence of neuropsychiatric events attributed to the use of mefloquine mainly occur during the early use of this prophylactic agent, we stratified for duration of residence in the endemic area (table 3). A statistically significant difference in TMD *between* Malarone and mefloquine users was observed within the tertile of shortest residence in the endemic malaria area, and *within* mefloquine users was observed within the shortest and intermediate tertiles of residence in the endemic malaria area (table 3).

Because a low BMI may be a risk factor for neuropsychiatric adverse events during the prophylactic use of mefloquine, we examined the change in scores within strata of BMI (≤25, >25). A significant difference *between* Malarone and mefloquine was observed on the domains depression, fatigue and TMD in the lowest BMI category. In the highest BMI category, we observed no differences *between* the two treatment arms (table 3).

Table 4 Scores on the NES

	Score		Mean difference		p-value*	p-value**
	t0	t1	t1-t0	[95%CI]		
Malarone						
Continuous performance (msec)	375	388	13	[3, 24]	0.959	**0.012**
Hand-eye co-ordination (log RMSE)	1.95	1.73	-0.22	[-0.29, -0.15]	0.749	**<0.001**
Coding speed (sec/dig)	2.13	2.02	-0.11	[-0.16, -0.05]	0.904	**<0.001**
Mefloquine						
Continuous performance (msec)	377	390	13	[3, 23]	0.959	**0.008**
Hand-eye co-ordination (log RMSE)	1.80	1.62	-0.18	[-0.23,-0.12]	0.749	**<0.001**
Coding speed (sec/digit)	2.14	2.09	-0.06	[-0.10, -0.01]	0.904	**0.011**

*p-value between treatment arms

**p-value within treatment arm

Statistically significant differences printed in bold

However, within mefloquine users there was significant deterioration in the domains of fatigue, vigour and TMD for both BMI strata.

Table 4 shows the results of change in NES scores between the two treatment arms. We observed changes in continuous performance during the use Malarone with an increase of 13 msec [95%CI: 3, 24] as well as during the use of mefloquine with an increase of 13 msec [95%CI: 3, 23]. Stratification for gender and adjustment for possible confounders such as use of coffee, tea and smoking did not affect the results. The change in reaction time was higher upon increased duration of stay (table 4a).

Table 4a Continuous performance stratified for duration of residence

	Number of users		Mean change in score [95%CI]		p-value*	p-value**	
	Malarone	Mefloquine	Malarone	Mefloquine		Malarone	Mefloquine
CPT							
Duration of residence							
≤16 days	30	18	9 [0.2, 17]	1 [-12, 14]	0.300	**0.044**	0.846
17-22 days	16	23	11 [0.7, 21]	17 [3, 30]	0.507	**0.038**	**0.016**
≥22 days	15	15	25 [-15, 65]	23 [-5, 54]	0.906	0.199	0.106

Statistically significant differences printed in bold

*p-value between treatment arms

**p-value within treatment arm

This relationship was not statistically significant and there were no differences between Malarone and mefloquine (table 4a). Stratification for BMI showed that in both treatment arms reaction time was significantly increased in subjects with a BMI ≤25kg/m^2, and reaction time was not affected in subjects with a BMI>25. Within the BMI categories, there was no difference between Malarone and mefloquine users regarding reaction time.

The hand-eye-co-ordination task and coding speed improved significantly between the first and second measurement in both treatment arms. Between the two treatment arms, however, no differences were observed.

Discussion

In this study, we compared the occurrence of neuropsychiatric adverse events and concentration impairment between mefloquine and Malarone. The most important findings in this study were the significant difference in change in

POMS score between Malarone and mefloquine. Whereas mefloquine users deteriorated significantly, Malarone did not affect mood. This effect occurred during early use only and mostly in women.
Our measures of concentration impairment showed no significant difference in change between Malarone and mefloquine users. Within subjects, continuous performance decreased significantly for both mefloquine and Malarone, an effect that increased upon longer use of the drugs and was not affected by gender or BMI, but hand-eye co-ordination and coding speed improved in both groups.
In the Netherlands, mefloquine is currently the prophylactic drug of choice for travellers staying more than seven nights in areas of high risk of exposure to chloroquine-resistant falciparum malaria (17). During the last years, case reports on CNS adverse events, and widespread media attention regarding CNS effects has influenced the clinical and public opinion on the use of mefloquine (18-21). The spontaneous reports on dizziness, dysphoria, light-headedness, and difficulty in concentrating have resulted in a relative contraindication for mefloquine in persons involved in tasks demanding fine co-ordination and spatial discrimination (air crews) in the Netherlands (17), and is incorporated in a WHO clause.

Malarone has proven to be safe and effective for the treatment of acute, uncomplicated, falciparum malaria, and has been approved for the treatment of falciparum malaria in more than 35 countries. Clinical studies conducted in highly endemic countries in east, west and southern Africa have shown that Malarone is efficacious and safe for the chemoprophylaxis of falciparum malaria in both adults and children (6). Because the areas in which both drugs will be used are the same, the safety profile of Malarone should be equal and preferably better than the safety of mefloquine. We did not observe neuropsychiatric adverse events during the use of Malarone, whereas during the use of mefloquine significant deteriorations of mood were observed. As the study was double-blind, these findings can not be explained by information bias of the participants or observation bias by the researchers.

Previous studies on the neuropsychiatric adverse events during the prophylactic use of mefloquine have been inconclusive. Some authors have suggested that the physiological and psychological stress of intercontinental travel may be of importance for mefloquine-associated adverse events (22, 23). Furthermore, several studies have reported a higher cumulative incidence of

neuropsychiatric adverse events in women than in men (22, 24-27). In this prospective, double-blind and randomised study, the potential confounding effect of travel and travel destination has been controlled for by the use of a comparator arm. Our results suggest that neuropsychiatric adverse events are attributable to the use of mefloquine and do not occur during the use of Malarone, or occur to a much lesser extent. The results of this study also demonstrate the occurrence of neuropsychiatric adverse events during the use of mefloquine in males. This is in contrast with previous findings from our group. In previously performed studies, we identified gender and a low BMI as effect modifiers for the occurrence of neuropsychiatric adverse events during the first three weeks of use of mefloquine. We also observed significantly lower mefloquine serum levels in males than in females after intake of three tablets. A possible explanation for this seemingly contradictory result might be the difference in follow-up time. In the current study, the change in mood was measured over a mean period of 46 days. In the previous study, we looked at early effects on mood and concentration namely during the three week run-in period prior to departure. The effect on mood might be challenged by a steep increase in serum concentration of mefloquine or the passage of a certain threshold. Differences in pharmacokinetics between males and females might be responsible for a less steep increase in serum levels of mefloquine or for reaching the postulated threshold after a larger number of tablets in males.

Since, apart from changes of mood, concentration impairment has been reported frequently during prophylactic use of mefloquine and has resulted in a WHO clause, we compared the reaction time in users of both drugs. We observed a statistically significant increase in continuous performance reaction time within subjects in both treatment arms, but no differences in change between the two groups. In both treatment groups, the increase in reaction time progressively increased as the duration of travel increased, suggesting the change might be related to travel rather than to chemoprophylaxis. Such an effect would explain why we failed to show an effect in previous studies on mefloquine that measured changes after 3 weeks of treatment before departure.

The results of the coding speed and hand-eye-co-ordination tasks showed that both treatment arms improved at the second measurement. This is most likely attributable to the learning effects of these tasks. The learning effect is known to be most pronounced between the first and second measurement (16).

In conclusion, we observed significant mood changes only in mefloquine users and not in Malarone users. As these two drugs have similar efficacy for malaria prophylaxis, this makes Malarone a safe and effective alternative for mefloquine.

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8

General discussion

8

General discussion

The aim of the studies described in this thesis was to provide epidemiological insight into the occurrence of and risk factors for neuropsychiatric events/symptoms during the use of malaria prophylaxis, and in particular mefloquine. In this chapter, the main findings of our and other studies will be summarised. In the previous chapters, shortcomings and merits of the individual studies have been addressed, but this chapter will discuss the general methodological issues inherent to the study of mefloquine-associated neuropsychiatric effects. In addition, the clinical relevance of our findings, and recommendations for future research will be made.

Background

In 1989, the first mefloquine-associated neuropsychiatric adverse effects were reported in the literature (1-4). Two years later, the rate of serious adverse effects was estimated to range from 1-5:10,000 users during prophylactic use and from 1:250 to 1:1,754 persons during therapeutic use (5, 6). In the period 1992-1995, the Drug Safety Unit of the Inspectorate for Health Care in the Netherlands received a total of 136 reports of neuropsychiatric effects attributed to the intake of mefloquine in a prophylactic dose of 250 mg weekly. The estimated number of reports ranged from 16-37 per 100,000 users. Because of substantial underreporting, the true incidence of neuropsychiatric adverse effects during prophylactic use of mefloquine was thought to be higher than the previously estimated incidences. Case reports on CNS adverse events and widespread media attention have influenced the public and clinical opinion on the use of mefloquine (6-9). The spontaneous reports of dizziness, dysphoria, light-headedness and difficulty in concentrating have resulted in a relative contraindication for mefloquine in persons involved in tasks demanding fine co-ordination and spatial discrimination in the Netherlands (10) and is incorporated in a WHO clause (11). Despite this, only three studies in selected populations have been conducted to determine the effects of mefloquine on performance. None of them could substantiate a negative impact of mefloquine (12-14).

The fact that the incidence of neuropsychiatric adverse events was unclear, that risk factors for the occurrence of these adverse events were unknown, and that a negative impact of mefloquine could not be substantiated in previous studies, stimulated us to initiate the work on which this thesis is based. The aim of the research was to estimate the risk of various neuropsychiatric adverse effects attributed to the use of mefloquine and to identify possible risk factors for these adverse effects.

Main findings

Utilisation of malaria prophylaxis

During the past years, guidelines for prescription of malaria prophylaxis have changed considerably. In chapter 2.1, we present a utilisation study in which we provide insight into the prescription patterns of malaria prophylaxis and into the adherence to the guidelines for malaria prophylaxis during the period 1993 to 1998. Before 1994, mefloquine was recommended as malaria prophylaxis only for a limited number of geographical areas. In 1994, the number of areas for which mefloquine was recommended increased (15, 16). Our data showed that the number of prescriptions of mefloquine as well as the number of prescriptions of mefloquine per 1000 travellers increased in the period 1994-1995. In 1996, the period that mefloquine should be taken prior to departure (run-in period) was extended from one to three weeks. This was done in order to obtain effective prophylactic blood levels and to allow for the detection of possible adverse effects that mostly occur during early use of mefloquine (17, 18). Our data did not show an absolute increase in duration of use of mefloquine. This may be explained by shorter duration of travel, since comparison with proguanil (that does not require a run-in period) showed that the mean difference in duration changed from about 1 week in 1994 to approximately three weeks in 1998.

In 1998, guidelines were updated again because of increasing resistance of *P. falciparum* against mefloquine and because of the publicity about the potential adverse effects during prophylactic use of mefloquine (19, 20). For short trips, the use of proguanil plus chloroquine was advised, or in some cases, travellers could even avoid use of malaria prophylaxis. Our data showed that until 1997, the use of mefloquine exceeded the use of proguanil, but in 1998 proguanil was used more frequently. The results of this utilisation study showed that healthcare

providers adequately followed guidelines regarding the prevention of malaria in non-immune travellers.

Neuropsychiatric adverse events attributed to mefloquine

In Chapter 3 we describe all reports and the follow-up of the reports of neuropsychiatric effects attributed to the prophylactic use of mefloquine as reported to the Drug Safety Unit of the Inspectorate for Health Care in the Netherlands during the period 1992-1996. The reports pertained to young individuals without a psychiatric history and concerned mainly anxiety, depression, agitation, concentration impairment and insomnia. The clear temporal relationship is in strong support of a causal relationship. Additional information on clinical characteristics and risk factors were collected from the patients through the reporting physician. This information showed that adverse effects occur mainly during the first three weeks of use and subsequently vanish or diminish. Assessment of the psychological status showed that this was comparable to the pattern observed in outpatient psychiatric patients.

Neuropsychiatric effects of antimalarials during travelling

Although several studies and case reports have suggested that the use of mefloquine is associated with the occurrence of neuropsychiatric adverse events (1, 2, 6, 7, 9, 21-24), data on the frequency of these effects are scanty. The prospective cohort study among travellers described in chapter 4 showed that the risk of insomnia and palpitations was associated with the use of mefloquine. The risk was highest in women, and especially in women using alcohol concomitantly with mefloquine. The predominance of the effects in females was in line with other published studies (7, 12, 25, 26). Since the follow-up period included stay in the tropics, the confounding effect of travel destination, and the hypothesised effects of physiological and psychological stresses of intercontinental travel could not be excluded (27). In order to estimate the risk of psychiatric events during the use of mefloquine relative to non-use of malaria prophylaxis while controlling for the distorting effects of travel destination, we performed a case-control study, among persons travelling outside Europe and contacting an alarm centre for psychiatric symptoms and other medical complaints during travelling (chapter 5). Through matching on continent we controlled for the confounding effects of travel destination. In this study we

observed an association between the use of mefloquine and the occurrence of psychiatric symptoms in females. Despite the fact that mefloquine is contraindicated in persons with a history of psychiatric diseases (10), the drug was prescribed to persons with this contraindication which gave rise to a high risk of relapses in this group of patients.

Early adverse effects of mefloquine

Although we tried to control for the confounding effects of physiological and psychological stress related to travel in the study described in chapter 5, we could not exclude residual confounding related to country of travel and type of travelling. In order to exclude the effect of travelling, we initiated a second series of studies that aimed to investigate the neuropsychiatric effects of mefloquine during the run-in period. In chapter 6, we describe the results of a cohort study among mefloquine users that aimed to assess the occurrence of concentration impairment and neuropsychiatric effects during the period between baseline (no exposure) and the end of run-in period (three weeks) but always prior to departure. We observed a higher incidence of neuropsychiatric adverse events than were reported in previously published papers (12, 13, 24). The adverse events occurred predominantly in first time female users (chapter 6.1), and were further modified by BMI (chapter 6.2). Persons with a low BMI encountered neuropsychiatric adverse events more frequently than persons with a high BMI. Especially first time female users with a low BMI were at high risk for encountering these adverse events (chapter 6.2). With respect to concentration impairment, we did not show an overall association between the early use of mefloquine and a change in reaction time. However, after stratification for gender and BMI, we observed that women with a low BMI increased significantly in their reaction time (chapter 6.2).

Serum levels of mefloquine and early adverse effects

The effect of BMI demonstrated in chapter 6.1 and 6.2 suggested the possibility of a concentration-effect relationship, since mefloquine is prescribed in a fixed dose. Mefloquine is distributed extensively in the tissues and is eliminated slowly. Considerable inter-individual differences in pharmacokinetic parameters have been reported (21). It has been speculated that the parent compound (4) as well as its carboxylic acid metabolite may play a role in the occurrence of the

adverse effects (28). However, no relationship between the serum levels of mefloquine as well as its main metabolite and CNS adverse effects has been shown previously (12). The relationship between serum levels of mefloquine and the occurrence of early neuropsychiatric adverse events observed in our study is described in chapter 6.3. Our data showed that after three tablets of mefloquine, women had a significantly higher serum level of mefloquine than men. Independent of gender, serum levels were higher in persons with a high BMI. The serum level of the carboxylic acid metabolite was inversely related to BMI. The serum level of mefloquine was significantly higher in subjects reporting adverse events. In an attempt to explain the relationship between neuropsychiatric effects, gender, BMI and serum concentration of mefloquine, we hypothesise that especially women with a low BMI may receive initial doses which are relatively too high and a cause of neuropsychiatric adverse effects. More studies on the pharmacokinetics should be performed in persons with a low BMI.

Atovaquone plus proguanil versus mefloquine for malaria prophylaxis

Resistance of *P. falciparum* against currently available chemoprophylaxis is increasing which causes major problems in the prevention and treatment of malaria. Recently, a new antimalarial combination Malarone (atovaquone 250 mg and proguanil 100 mg, 1 tablet daily) was developed and tested. In chapter 7, we describe a prospective, double blind randomised study that compared the occurrence of neuropsychiatric adverse events and concentration impairment during prophylactic use of mefloquine and Malarone, respectively. This study was performed as a sub-study of the MAL30010 trial conducted by Glaxo Wellcome. The use of mefloquine was associated with mood disturbances whereas Malarone did not affect mood. Concentration impairment was shown both in mefloquine and Malarone users. The effect increased upon longer use of the drugs and was not affected by gender or BMI. The most likely explanation for this finding is that concentration impairment occurs during travelling irrespective of the use of chemoprophylaxis and may be a result of travelling itself. The chance that both drugs cause similar concentration impairment can not be excluded but is less likely. On the other hand, neuropsychiatric adverse events may be attributed to the use of mefloquine and can not always be explained by travelling itself.

Methodological considerations

Study design

In epidemiology, there are several study designs to estimate frequency of occurrence and measures of association. The studies described in this thesis range from descriptive (chapter 2.2 and chapter 3) to analytical (chapter 4-7). Analytical studies can be divided into observational and intervention studies.

In observational studies, the natural course of events, with respect to exposed and non-exposed subjects and the association with the outcome of interest is mostly studied through a case-control or cohort design. The disadvantages of a cohort study are that it is not efficient for the evaluation of a rare outcome, that it can be expensive and time consuming and that the validity can be seriously affected by "loss to follow-up". As compared to a cohort study, a case-control study is less time consuming and more cost efficient and it allows for easier assessment of multiple risk factors. A case-control design is a suitable design when the outcome is rare and the exposure(s) under study are relatively frequent. However, the temporal relationship between exposure and disease may be difficult to establish. Due to the often retrospective nature of a case-control study the internal validity may be more easily threatened by selection and information bias than a cohort study (29-31).

Internal validity

In this thesis, we attempted to estimate the association between neuropsychiatric disturbances and the use of mefloquine. In trying to do so we have faced all potential threats to the internal validity of observational studies that we will describe type by type.

Selection bias

Selection bias occurs when the association between the determinant and the outcome is different for those who participated and those who would be eligible for study. It is a particular problem in *ad hoc* case control studies, since exposure and disease have both occurred at the time subjects are selected for study, but it may also threaten the validity of a retrospective and prospective cohort study. An important cause of selection bias in field studies is non-response.

Non-responders may differ from responders with respect to risk factor status, socio-economic status and health status. In terms of relative risks, the association between exposure and outcome will be distorted only if the non-response is non-random with respect to both exposure and outcome. Since we could only study the neuropsychiatric effects of mefloquine through field studies, we have made substantial effort to minimise selection bias due to non-response and to evaluate its effects. In all studies, we have telephoned non-responders and asked for reasons of dropping out or non-response, their exposure status and/or their disease status. Invariably, non-response seemed random since non-responders had forgotten to complete the questionnaire or refused participation for reasons that were not related to the research questions. We never observed an association between non-response and both outcome and exposure.

Information bias

Another threat to the internal validity of an epidemiological study is information bias. Information bias may occur when there are systematic errors in the way exposure or outcome are assessed. Information bias that is random (errors in either disease or exposure measurement are independent from each other) will generally lead to an underestimation of the association, whereas differential errors of either disease and or exposure measurement will lead to unpredictable results.

Misclassification of disease

Misclassification of disease occurs due to the inclusion of false positive cases in the case series and false negative controls in the control series. Our outcome of primary interest pertained to neuropsychiatric disturbances, an outcome that is hard to define, difficult to measure and to quantify objectively. We have used several outcome measures in order to objectively assess the outcome. In chapter 5, we identified cases from persons calling alarm centres for medical help. In order to assess the presence of misclassification of disease, we performed three sensitivity analyses. The result of these analyses showed that by decreasing the false positive rate, the association became stronger, and therefore, misclassification did not change the conclusions of our study.

In chapter 6, we have used standardised scales to measure mood and concentration impairment. Despite the fact that these objective measures

decrease both the false negative and false positive rate, we cannot exclude small differential errors since subjects were compared with themselves. Differential errors could have occurred due to learning effects, leading to different specificities and sensitivities of the instrument prior to starting mefloquine and thereafter.

Misclassification of exposure

In both our case-control and cohort studies, we used data on self-reported use of mefloquine. In chapter 4 and 5, data on use of malaria prophylaxis was collected retrospectively by means of a questionnaire. Misclassification of exposure in case-control studies may occur when there are differences in the way exposure information is remembered or reported by cases and by controls (recall bias). In order to avoid a decreased recall in the case-control study described in chapter 5, we have sent questionnaires within a month after the anticipated date of return to both cases and controls. Although misclassification may be limited, we cannot rule out any differential error since neuropsychiatric adverse effects are specified in the data sheet of mefloquine. The fact that these effects have been discussed in the medical literature and lay press, however, makes it likely that cases and controls had a similar awareness of the occurrence of mental disturbances during use of mefloquine. For these reasons, and because controls also had a serious medical reason for contacting the alarm centre, substantial bias is unlikely.

In chapter 6, we limited ourselves to mefloquine users and looked at the early exposure (prior to departure) and asked for prospective data collection on intake by means of a diary. In addition, we assessed the serum levels of a subset of patients. This revealed that all subjects had been exposed to mefloquine. Although serum concentration of mefloquine is a more useful exposure measure since it is closer to the ultimate exposure that should be studied (i.e. concentration at the site where it causes the effect) it is still not perfect. None of the previously conducted studies had been able to relate the serum concentration of mefloquine to the occurrence of neuropsychiatric effects. This may be due to the fact that the actual exposure of interest, namely concentration in the brain cannot be measured.

In chapter 7, we used pill counts to assess compliance to either Malarone, placebo or mefloquine. The compliance with the study drugs was high and therefore misclassification of exposure was not likely.

Confounding

Confounding is a distortion in the estimated exposure effect that results from differences in risk between the exposed and unexposed that are not due to exposure. Before a variable is considered a confounder, it must be an independent risk factor for the disease among the unexposed, associated with the exposure variable in the source population from which the subjects are derived, it must not be affected by the exposure or the disease, and it cannot be an intermediate step in the causal path between exposure and the disease. There are several methods to control for confounding, including randomisation (design), restriction (design), matching (design and analysis) and adjustment for the potential confounder (analysis). In order to be able to control for confounding in the analysis, information on the potential confounder should be obtained (29-31).

Factors that may act as potential confounders in studies on the relation between the use of antimalarials and neuropsychiatric disturbances are age, gender, history of psychiatric disturbances, destination of travel, travelling alone, time zone changes and history of use of antimalarials. These are all strongly correlated with the occurrence of neuropsychiatric disturbances and the use of antimalarials. In the studies presented in this thesis, we tried to eliminate the effects of these potential confounders in several ways. In chapter 4 and 6 the analyses were statistically adjusted for potential confounders. In chapter 6, we restricted to mefloquine users and eliminated between subject confounding by conducting a cross-over analysis. Although we controlled for constant subject characteristics by design, the cross-over was always into one direction and therefore we could not exclude the effects of pre-travel stress. In chapter 5, we matched on travel destination and adjusted for the other potential confounders, whereas in chapter 7, randomised allocation to Malarone or mefloquine was used to control for confounding by design.

A specific type of confounding, which was encountered in chapter 6, is confounding by contraindication resulting from *depletion of susceptibles* in regular users. This type of confounding occurs when past experience with the drug influences the risk of an adverse outcome associated with current use. Patients who have used the drug before, may not be at the same risk as first time users of the drug. At the population level, it will result in the phenomenon *depletion of susceptibles* whereby patients who tolerate the drug will use it again

while those who are susceptible select themselves out of the population at risk (32). The selection of the cohort, as presented in chapter 6 is based on the prescription of mefloquine to persons planning to make a trip to a tropical area for which mefloquine is advised. The traveller is examined by a nurse and during the visit the choice of chemoprophylaxis is made, based on the absence of contraindications for the drug and the visited tropical area. This leads to a selection of a relatively healthy cohort formed by all first time users (with no known contraindications for the drug) and travellers who had used mefloquine before and who did not encounter adverse events. Upon stratification for previous use of mefloquine we observed that first time users of mefloquine had a larger increase in the total score of the POMS than users who had used mefloquine before.

Clinical relevance

It is known that travelling may cause psychiatric disturbances and may aggravate psychiatric illness. Several risk factors for psychiatric syndromes during travelling have been proposed, including travel destination, travelling alone, route of transportation and time zone changes. Furthermore, the use of malaria prophylaxis may be of importance for the occurrence of these complaints (33-35). As malaria is a potentially life-threatening disease, the prevention of malaria in travellers is important.

Mefloquine is a commonly prescribed antimalarial drug, effective against all Plasmodium species, but the use of mefloquine may be associated with neuropsychiatric adverse effects (36). In this thesis, we explored the effects of mefloquine on the occurrence of psychiatric disturbances before and during travelling.

By using objective outcome assessments and different study designs, we were able to quantify the effect of mefloquine on mood and performance and to study the relationship between serum levels of mefloquine and the occurrence of neuropsychiatric adverse events. Furthermore, our studies are generalisable, since they were performed in subjects who were either already travelling or were planning to make a trip to the tropics.

Our most important observations are that the risk seems to be more pronounced in women and persons with a low BMI. Previously performed studies also showed that women are more likely to experience adverse events (7,

12, 25). There are two potential explanations for this observation. First, women might perceive adverse events more readily than men and/or men might dissimulate such events. Second, the events might be dose-related, since all persons use a fixed dose despite large differences in height and weight. Although we can not discard the first option completely, the fact that also severe psychiatric disturbances occurred more frequently in women makes this explanation less likely. Moreover, the fact that women had a stronger increase in reaction time suggests a physical basis for the events.

None of the studies in the literature could demonstrate an association between serum levels of mefloquine, BMI and adverse events (12, 25). We observed differences in serum levels of mefloquine between males and females which were independent of BMI and within BMI categories were independent of gender. We were also able to show an association between serum levels of mefloquine and the occurrence of neuropsychiatric adverse events. Since the bioavailability of mefloquine is improved by normal food intake this may partly explain the differences observed in serum levels between the different BMI categories (37). Apart from the fact that persons with a low BMI have a smaller volume of distribution, they may also have less food intake than persons with a high BMI.

How do these findings fit together, and how does mefloquine cause neuropsychiatric adverse effects? Mefloquine has acetylcholinesterase inhibiting properties, and stereospecific inhibition of acetylcholinesterase (the (-)-enantiomere is a more potent acetylcholinesterase inhibitor than the (+)-enantiomere) has been reported (38, 39). It is known that acetylcholinesterase inhibitors are able to affect the central nervous system resulting in anxiety, restlessness, disrupted concentration and memory, confusion, sleep disturbances, and convulsions (40). Hence, the adverse reaction profile of mefloquine is compatible with its pharmacological activity. But why do persons with a low BMI develop these reactions more readily despite a lower blood level? One of the explanations may be that in persons with a low BMI more of the highly lipid-soluble drug mefloquine will reach the brain during the first distribution phase than in persons with a high BMI. Highly lipid-soluble drugs generally require only a single passage of blood through an organ to establish a blood-tissue equilibrium (41). The brain comprises only 2% of body weight but receives 12% of the cardiac output while adipose tissue comprises approximately 20% of body

weight in an adult of average weight but receives only 10% of the cardiac output (41). As mefloquine is given in a fixed dose, it is reasonable to assume that in persons with a low BMI higher levels of mefloquine reach the brain than in persons with a high BMI who will distribute more mefloquine to their adipose tissues. This is reminiscent of the principle that fat persons require more of an anaesthetic to induce anaesthesia but have a prolonged recovery phase because the anaesthetic agent is slowly released from adipose tissues. The low mefloquine/carboxylic acid metabolite ratio might result from a higher extraction ratio in persons with a low BMI induced by initially higher serum levels of mefloquine. A different dosing scheme, for example starting with 125 mg twice weekly, may possibly diminish the occurrence of adverse events. Due to the long elimination half-life of mefloquine, steady state concentrations of mefloquine will not substantially be affected and the effectiveness of the prophylaxis will not be compromised.

The reports of possible effects of mefloquine on performance have resulted in a WHO clause restricting the use of mefloquine in individuals involved in tasks requiring fine co-ordination and spatial discrimination (42). This clause may have many ramifications, not just for pilots and military personnel, but also for car drivers and divers. The study presented in Chapter 6 showed no association between the use of mefloquine and an increase in reaction time, except in women with a low BMI. The clinical trial presented in Chapter 7 suggested, however, that the increase in reaction may also be a result of travelling itself. Furthermore, our data suggest that an increase in reaction time depended on the duration of stay in the tropics independently of the type of malaria prophylaxis.

The key issue in recommending malaria prophylaxis for healthy persons remains tolerability. Poor tolerability may lead to diminished compliance and thereby result in malaria breakthrough (19). Since every year, ten thousands of travellers will encounter mild to severe neuropsychiatric adverse events during the use of mefloquine, physicians who prescribe mefloquine will have to inform travellers about the pro and cons of using mefloquine, and should offer an alternative chemoprophylaxis to users encountering adverse events.

An effective and probably safe alternative to mefloquine may be the combination of atovaquone and proguanil. However, until this drug is registered for prevention of malaria, mefloquine remains an important drug for prophylaxis and treatment of malaria.

Recommendations for future research

In this thesis, the incidence of adverse events during the prophylactic use of mefloquine was higher than reported in the literature. Especially mild to moderate neuropsychiatric adverse events are common during use of mefloquine. Furthermore, our data showed that the incidence during use of mefloquine was also higher than during the use of proguanil. Studies published in the literature provide heterogeneous results, mainly caused by differences in study design, methodologies, definitions and populations. The published study designs range from database analyses and traveller surveys to controlled, double blind studies. Methodologies range from the administration of questionnaires and interviews to psychomotor test batteries. The populations studied range from military personnel to tourists (6, 13, 23-25, 43, 44).

Due to all these differences, it is difficult to compare the risks and associations observed in these studies. In order to be able to compare studies, some consistency regarding outcome measures and target population should be aimed at, and the design of future studies should take this into account. Therefore, we focused on consistency with respect to methodology and study populations.

Despite the fact that we were able to identify female gender and low body mass index as effect modifiers for the occurrence of neuropsychiatric adverse events during the use of mefloquine, and the association between serum levels of mefloquine and the occurrence of these events, several questions remain unanswered and should be addressed in future research. First, what are the reasons for the gender-related differences in the pharmocokinetics of mefloquine? In order to answer this question, further research into the physicochemical properties of the drug, its protein binding characteristics and the role of the enterohepatic circulation will be required. Second, in view of the reported stereoselective pharmacokinetics of mefloquine and the selective passage of the -(-) enantiomere into rat brains, and the potential association with the occurrence of neuropsychiatric adverse events (12, 45, 46), more information should become available on the distribution of mefloquine and the two enantiomeres between blood, fat and brains. Furthermore, because the (-)-enantiomere is thought to be responsible for the occurrence of adverse effects and the (+)-enantiomere is thought to be the active compound (47), future research should focus on the formulation of a tablet containing only the (+)-

enantiomere. Another and maybe more readily available option might be to study the efficacy and effectiveness of twice weekly doses of 125 mg in order to avoid high peak levels.

Apart from the remaining questions about the properties of mefloquine, future research should also focus on other drugs or combinations of drugs that may be effective for prevention and treatment of malaria. A potential safe and effective drug seems to be the combination of proguanil and atovaquone (Malarone). Malarone has already been approved in Denmark for the prophylaxis of *P. falciparum* malaria, and recently, the FDA has approved this drug for the prevention and treatment of acute uncomplicated malaria. Before approval, Malarone has been evaluated in semi-immune subjects, and despite the fact that the results of the safety and efficacy trial in non-immune subjects had not yet been reported, this drug has been approved (48-52).

From the results presented in chapter 7, it may be concluded that the frequency of neuropsychiatric adverse events during the use of Malarone is lower than during the use of mefloquine. Although Malarone seems to be tolerated better than mefloquine, we do not think that it can replace mefloquine within a short period of time. The dosing scheme of mefloquine (once weekly) may be more convenient for travellers than the dosing scheme of Malarone (daily), the tolerability of Malarone has not yet been studied in periods of use of longer than 28 days and it is more expensive than mefloquine.

Another potentially effective drug seems to be tafenoquine. It has been studied in semi-immune subjects and is reported to be safe and effective (53, 54). The optimal dosage of tafenoquine is not yet known, however, it was found to be effective against *P. falciparum* infections for 77 days after taking 250 mg on three consecutive days. In terms of convenience and compliance, this drug may be useful for travellers visiting malaria endemic areas for short periods of time. However, before this drug is approved and distributed, further research on the effectiveness and tolerability should be performed and therefore, in the meantime, mefloquine may remain an important drug in malaria prevention.

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9

Summary

9.1

Summary

Malaria is a serious, potentially life threatening disease, and generally endemic in the (sub) tropics. The prevention of malaria is of importance in travellers to those areas and may be carried out by interrupting transmission, by vector control and by giving travellers prophylactic drugs. The increase in international travel from temperate to tropical areas and the increase in resistance of *P. falciparum* against the available agents, has led to the development of mefloquine, an effective drug for both the prevention and treatment of malaria. However, mefloquine use seems to cause neuropsychiatric adverse effects relatively frequently. The aim of the studies described in this thesis was to provide epidemiological insight into the occurrence of and risk factors for neuropsychiatric events /symptoms during the use of malaria prophylaxis, and in particular mefloquine.

In **Chapter 2.1** an overview is presented of the pathogenesis, diagnosis and treatment and prophylaxis of malaria. Because of an increase in international travel from temperate zones to tropical countries and increasing drug resistance of *P. falciparum* a growing number of travellers are at risk for contracting malaria. In order to prevent malaria in travellers, guidelines for malaria prophylaxis and adherence to these guidelines is important. In **Chapter 2.2** we gave insight into dispensing patterns of malaria chemoprophylaxis and determined whether health care providers have followed changes in guidelines. Data on prescriptions of proguanil and mefloquine were obtained from the Dutch "Foundation for Pharmaceutical Statistics" (SFK) covering the period January 1st 1993 up to December 31st 1998. From the Statistics Netherlands (SN) we obtained the number of travellers to endemic areas during the years 1994-1998. The total number of prescriptions for malaria chemoprophylaxis increased during the period 1993-1997, whereas the number of prescriptions per 1000 travellers decreased over the years. The increased run-in period appeared to be taken into account by prescribers. We observed small differences in the prescription rate of prescriptions for mefloquine between geographical regions in the Netherlands. We concluded that changes in the guidelines of malaria

prophylaxis with respect to type and duration were followed by health care providers.

In **Chapter 3.1** we described 136 reports of neuropsychiatric effects to mefloquine, notified since 1992 to the Inspectorate for Health Care in the Netherlands. The most important effects reported were anxiety, depression, restlessness and agitation, nightmares, insomnia and concentration impairment. In more than 80 percent of the cases, the first symptoms appeared within the first 3 weeks of intake of mefloquine. We concluded that the neuropsychiatric effects of mefloquine are probably caused by a neurotoxic effect of the drug or, one or more of its metabolites. The frequency seems to be higher during use of mefloquine than during use of other antimalarial drugs.

In **Chapter 3.2** we described the follow-up of the patients reporting neuropsychiatric adverse effects attributed to the prophylactic use of mefloquine to the Inspectorate for Health Care. Data were collected by means of a mailed questionnaire. Information on the use of drugs, alcohol, coffee, smoking, general health and medical and psychiatric history was obtained. To make an objective assessment of the presence of psychiatric effects and the severity of these effects we used the domains anxiety, depression, and insufficiency of thinking and action, sleeping disturbances and hostility from the validated Dutch Symptom Checklist-90 (SCL90). As compared to a normal male reference population, males scored significantly higher on the domains sleeping disturbances, insufficiency of thinking and action, depression and anxiety. Our female study population scored significantly higher on the domains sleeping disturbances, depression and anxiety than the normal female reference population. As compared to an outpatient psychiatric reference population, no differences were observed. The conclusions of this follow-up were that adverse effects attributed to mefloquine occurred mainly during the first three weeks of use of mefloquine and subsequently vanish or diminish. Furthermore, one of the most important results of this study was the finding that the psycho-pathological pattern of neuropsychiatric disturbances during the use of mefloquine is not different from the pattern of outpatient psychiatric patients.

In order to study the neuropsychiatric effects occurring during travelling, we performed a cohort and a nation-wide case-control study. In **Chapter 4** a prospective cohort study among travellers is described, aiming to investigate the neuropsychiatric adverse effects of antimalarial drugs. The final population

consisted of 394 users of mefloquine, 493 users of proguanil and 340 persons not taking any antimalarials. We observed that insomnia was most frequently encountered in users of mefloquine and mouth ulcers in users of proguanil. After adjustment for gender, age, destination, and alcohol use, the risk of insomnia to mefloquine versus non-users of antimalarials was 1.6, and the excess risk was 6 per 100 users over an average period of 2 months. Stratification by gender demonstrated that insomnia was more common in women on mefloquine, but not in men. Also, women more frequently mentioned palpitations as an adverse event. After adjustment for age, destination, and alcohol use in women, the relative risks for insomnia and palpitations to mefloquine versus non-use of antimalarials were 2.4, and 22.5, respectively. When travellers were specifically asked for the adverse reactions they had experienced, anxiety, vertigo, agitation, and nightmares were significantly more frequently mentioned by mefloquine users.

Since the follow-up period of the previous study included a stay in the tropics, the confounding effect of travel destination and the hypothesised effects of physiological and psychological stresses of intercontinental travel could not be excluded. In order to estimate the risk of psychiatric events during the use of mefloquine relative to non-use of malaria prophylaxis while controlling for the distorting effects of travel destination, we performed a nationwide case-control study, which is described in **Chapter 5**. In this study, we used the medical records of four large alarm centres in the Netherlands. Cases were patients contacting the alarm centres with psychiatric events. To every case we matched up to six controls that contacted the alarm centre for other medical reasons by alarm centre, calendar time and continent of travel. The study population consisted of 111 cases and 453 controls. As compared to non-use, the risk of psychiatric events during the use of mefloquine was 3.5 (1.4-8.7). The association was not statistically significant in males. In females, the risk was 47.1 (3.8-578.6). Stratification for history of psychiatric diseases showed that the risk of psychiatric events during use of mefloquine in subjects without a history of psychiatric diseases was 3.8 (1.4-10.1), whereas the risk in subjects with a history of psychiatric diseases was 8.0 (1.8-35.8). The use of proguanil was not associated with the occurrence of psychiatric symptoms in persons with and without a history of psychiatric disease. We concluded that the use of

mefloquine is associated with the occurrence of psychiatric events among women and is more pronounced in patients with a history of psychiatric diseases.

Although we tried to control for the confounding effects of physiological and psychological stress related to travel, we could not exclude residual confounding due to differences within continents. Therefore, we initiated a second series of studies that aimed to study the neuropsychiatric effects of mefloquine and the effects on concentration during the run-in period of mefloquine, prior to departure. For assessment of the neuropsychiatric effects we used the validated Profile Of Mood States (POMS) scale, for the assessment of concentration impairment we used the Neurobehavioural Evaluation System (NES) battery. In **Chapter 6.1** we described the results of a cohort study among mefloquine users that aimed to assess the occurrence of concentration impairment and neuropsychiatric effects during the period between baseline (no exposure) and the end of the run-in period (three weeks) but always prior to departure. Females reported adverse events more frequently than males (p=0.005). Overall, we observed a small but significant increase in the score on the domain fatigue of the POMS scale. The effect was exclusively present in females and not in males. First time users of mefloquine increased in Total Mood Disturbance (TMD) and among those, women showed the largest increase. We observed no changes in the continuous performance score during follow-up. The hand-eye-co-ordination task and coding speed improved significantly between the first and second measurement.

In **Chapter 6.2** we described risk factors for neuropsychiatric adverse events and concentration impairment in the cohort of mefloquine users. We observed that Body Mass Index (BMI) as well as gender modified the risk for these adverse events. Stratification for BMI showed that the Total Mood Disturbance in females in the lowest BMI category increased, whereas BMI did not affect the risk in males. Further stratification for history of use of mefloquine demonstrated that first time female users with a BMI $\leq$ 20 kg/m^2 deteriorated even more. An increase in reaction time was observed only in the lowest BMI tertile of the total population. Stratification for gender showed that women with a BMI $\leq$ 20 kg/m^2 increased significantly whereas men did not change in their reaction time. Stratification on history of use showed that first time users of mefloquine with a BMI $\leq$ 20 kg/m^2 increased in their reaction time and that the increase was most pronounced in first time female users with a low BMI. We

concluded that gender and BMI were effect modifiers for mefloquine associated neuropsychiatric adverse events and concentration impairment.

The effect of BMI demonstrated in Chapter 6.1 and 6.2 pointed our attention to the possibility of a relationship between neuropsychiatric adverse events and the serum level of mefloquine. The study on this topic is described in **Chapter 6.3**. We investigated the association between serum levels of mefloquine, gender, BMI and the occurrence of neuropsychiatric adverse events. Females had a significantly higher serum level of mefloquine than males. Stratification on BMI showed that the serum concentration of mefloquine in females with a low BMI was significantly lower than in females with a high BMI. The serum concentration of the carboxylic acid metabolite was inversely related to BMI. The serum concentration of mefloquine was significantly higher in subjects with neuropsychiatric adverse events. We did not observe an association between the occurrence of neuropsychiatric adverse events and serum concentration of the carboxylic acid metabolite.

Since we restricted ourselves to mefloquine users in some of our studies to investigate the mechanisms, we learned little about the comparison with other antimalarials. Therefore, we performed a study within a Phase III, prospective, double blind, randomised clinical trial in which randomisation to Malarone (atovaquone and proguanil hydrochloride) or mefloquine was used performed. This study is presented in **Chapter 7** and aimed to compare the occurrence of neuropsychiatric adverse events and concentration impairment during the prophylactic use of mefloquine or Malarone. We observed a significant deterioration on the domains depression, anger, fatigue, vigour and Total Mood Disturbance (TMD) during use of mefloquine but not during use of Malarone. Stratification on duration of residence in the endemic area showed that deterioration of TMD in mefloquine users was greatest in the tertile of shortest residence. In both treatment groups, sustained attention deteriorated but coding speed and visuomotor accuracy improved after travel. The change in sustained attention was greater with increased duration of stay. The results indicated that Malarone is a safe alternative to mefloquine.

Chapter 8 reflects our main findings. Our studies on the neuropsychiatric adverse events during the prophylactic use suggested that the frequency of these events during the prophylactic use of mefloquine is higher than during the use of other antimalarials and that the risk is modified by gender and BMI, probably

because these factors relate to the pharmacokinetics and serum levels of mefloquine. Subsequently, we discussed the general methodological issues inherent to the study of mefloquine associated neuropsychiatric effects. In addition, the clinical relevance of our findings, and recommendations for future research were discussed.

9.2

Samenvatting

Malaria is een ernstige en potentieel levensbedreigende ziekte, die voornamelijk voorkomt in de (sub)tropen. Het voorkómen van malaria bij reizigers naar gebieden waar malaria voorkomt is belangrijk. De reiziger kan zich beschermen tegen malaria door kleding met lange mouwen en lange pijpen te dragen en door geneesmiddelen te gebruiken die het ontstaan van malaria tegengaan (malariaprofylaxe). De toename van het aantal reizigers naar de tropische gebieden en de toenemende resistentie van de veroorzaker van malaria (*Plasmodium falciparum*) tegen geneesmiddelen voor de preventie of behandeling van malaria heeft tot de ontwikkeling van mefloquine geleid. Mefloquine is een effectief geneesmiddel, zowel voor de preventie als voor de behandeling van malaria, maar lijkt veelvuldig neuropsychiatrische klachten te veroorzaken. Het doel van de onderzoeken in dit proefschrift was om inzicht te verschaffen in de frequentie van neuropsychiatrische effecten van geneesmiddelen tegen malaria en in de factoren, die hierop van invloed zijn. In het bijzonder wordt aandacht gegeven aan de neuropsychiatrische effecten van mefloquine, vooral ook omdat deze bijwerking in de afgelopen jaren veel maatschappelijke onrust veroorzaakte.

In **Hoofdstuk 2.1** wordt een overzicht gegeven van de pathogenese, diagnose, behandeling en preventie van malaria. Door de toename van het aantal reizigers en de toenemende resistentie van *P. falciparum* loopt een steeds groter aantal personen het risico om malaria te krijgen. De kans op malaria wordt zo klein mogelijk gehouden door het goed toepassen en naleven van de richtlijnen met betrekking tot malariaprofylaxe. In **Hoofdstuk 2.2** wordt een overzicht gegeven van het aantal voorschriften voor geneesmiddelen tegen malaria en is onderzocht of voorschrijvers de veranderingen in de richtlijnen volgden. De gegevens met betrekking tot het aantal voorschriften van de geneesmiddelen tegen malaria proguanil en mefloquine in de periode 1993-1998 werden verkregen van de Stichting Farmaceutische Kengetallen (SFK). De gegevens met betrekking tot het aantal reizigers naar (sub) tropische gebieden in de jaren 1994-1998, werden verkregen van het Centraal Bureau voor de Statistiek (CBS).

Wij zagen een stijging van het aantal voorschriften voor malariaprofylaxe in de periode 1993-1997. Het aantal voorschriften per 1000 reizigers daalde echter in deze periode. Voorts zagen wij dat de richtlijnen goed in acht leken te worden genomen door de voorschrijvers en zagen wij kleine regionale verschillen in het voorschrijfgedrag.

In **Hoofdstuk 3.1** wordt een beschrijving gegeven van 136 meldingen van neuropsychiatrische bijwerkingen tijdens het gebruik van mefloquine. Het betreft vermoedelijke bijwerkingen, die vanaf 1992 gemeld werden bij de sectie Geneesmiddelenbewaking van de Inspectie voor de Gezondheidszorg. De meest gemelde bijwerkingen zijn angst, depressie, rusteloosheid en agitatie, nachtmerries, slapeloosheid en concentratieverlies. In meer dan tachtig procent van de gevallen traden de eerste symptomen op binnen 3 weken na het begin van het gebruik van mefloquine. Neuropsychiatrische klachten tijdens het gebruik van mefloquine worden mogelijk veroorzaakt door een neurotoxisch effect van het middel of van een of meer afbraakproducten (metabolieten). Voorts lijkt de frequentie van deze bijwerkingen hoger te zijn dan tijdens het gebruik van andere geneesmiddelen tegen malaria.

In **Hoofdstuk 3.2** bespreken we de resultaten van een vervolgstudie bij deze patiënten. De gegevens zijn verzameld door middel van een enquête, waarin we vragen stelden over het gebruik van geneesmiddelen, alcohol en koffie, roken, de gezondheidstoestand en medische- en psychiatrische klachten in het verleden. Om de neuropsychiatrische klachten tijdens het gebruik van mefloquine te objectiveren maakten we gebruik van Symptoom Checklist-90 (SCL-90), een gevalideerde reeks van schalen voor het meten van angst, depressie, insufficiëntie in denken en handelen, slaapstoornissen en vijandigheid. In onze onderzoeksgroep scoorden mannen significant hoger op de schalen met betrekking tot slaapstoornissen, insufficiëntie in denken en handelen, depressie en angst dan een als normaal beschouwde mannelijke vergelijkingsgroep. De vrouwen in onze onderzoeksgroep scoorden significant hoger op de schalen slaapklachten, depressie en angst dan de als normaal beschouwde vrouwelijke vergelijkingsgroep. Wanneer de mannen en vrouwen, die neuropsychiatrische klachten hadden, vergeleken werden met een groep ambulante psychiatrische patiënten werden er geen verschillen aangetoond. Uit dit onderzoek concludeerden wij dat de neuropsychiatrische klachten tijdens het gebruik van mefloquine voornamelijk optreden tijdens de eerste drie weken van het gebruik

en daarna verminderen of zelfs geheel verdwijnen en dat het patroon van deze bijwerkingen niet verschilt van het profiel van ambulante psychiatrische patiënten.

Om de neuropsychiatrische klachten tijdens het reizen te onderzoeken hebben we een cohort onderzoek en een landelijk patiënt-controle onderzoek uitgevoerd. In **Hoofdstuk 4** beschrijven we een prospectief cohort onderzoek onder reizigers met het doel om de neuropsychiatrische effecten van geneesmiddelen tegen malaria te bestuderen. De onderzoeksgroep bestond uit 394 gebruikers van mefloquine, 493 gebruikers van proguanil en 340 reizigers die geen malariaprofylaxe gebruikten. Wij vonden dat slapeloosheid de meest voorkomende klacht was bij mefloquine gebruikers en mondzweren bij gebruikers van proguanil. Na correctie voor geslacht, leeftijd, reisbestemming en het gebruik van alcohol was het relatieve risico op slapeloosheid tijdens het gebruik van mefloquine 1.6 en het aantal extra gevallen van slapeloosheid ten gevolge van mefloquine 6 per 100 gebruikers. Stratificatie voor geslacht liet zien dat het verhoogde risico op slapeloosheid bij vrouwen optraden niet bij mannen. Voorts rapporteerden vrouwen vaker hartkloppingen als bijwerking tijdens het gebruik van mefloquine. Na correctie voor leeftijd, reisbestemming en het gebruik van alcohol bleek bij vrouwen het relatieve risico op slapeloosheid en hartkloppingen tijdens het gebruik van mefloquine 2.5, respectievelijk 22.5 te zijn. In het onderzoek werd tevens expliciet gevraagd of men bijwerkingen had ondervonden tijdens het gebruik van malariaprofylaxe. Angst, duizeligheid, agitatie en nachtmerries werden significant vaker gemeld door gebruikers van mefloquine dan gebruikers van proguanil.

Aangezien de resultaten van dit onderzoek verstoord konden worden door verschillen in reisbestemming en door de fysiologische en psychologische effecten van het reizen, werd daarnaast een landelijk patiënt-controle onderzoek uitgevoerd waarin het risico op neuropsychiatrische klachten tijdens het gebruik van mefloquine werd bepaald. Voor de mogelijk verstorende effecten van reizen en de reisbestemming werd gecorrigeerd door een vergelijkingsgroep te kiezen, met hetzelfde werelddeel als reisbestemming (**Hoofdstuk 5**). In dit onderzoek werd gebruik gemaakt van de medische gegevens van de vier grootste alarmcentrales in Nederland. Voor patiënten, die contact opnamen met een alarmcentrale vanwege psychische klachten, werden maximaal 6 controles geselecteerd die vanuit hetzelfde werelddeel contact opnamen met de

alarmcentrale wegens een niet-psychische medische reden. Het relatieve risico op neuropsychiatrische klachten tijdens het gebruik van mefloquine bleek 3.5 te zijn. Bij mannen was het risico niet significant verhoogd maar bij vrouwen in hoge mate met een significant verhoogd relatief risico van 47.1. Een voorgeschiedenis van psychiatrische klachten bleek het risico te verhogen. Het gebruik van proguanil was niet geassocieerd met het optreden van psychiatrische klachten.

Om de mogelijk verstorende effecten van het reizen volledig uit te sluiten, werd tevens een onderzoek verricht om het optreden van neuropsychiatrische klachten en concentratiestoornissen te meten tijdens de eerst drie weken van het profylactisch gebruik van mefloquine voorafgaand aan het vertrek naar het malariagebied. In **Hoofdstuk 6.1** bespreken we de resultaten van het onderzoek dat hiertoe in deze periode plaatsvond. Om de neuropsychiatrische bijwerkingen en concentratiestoornissen te objectiveren werd gebruik gemaakt van de gevalideerde Nederlandse versie van de Profile of Moods States (POMS), respectievelijk de Neurobehavioural Evaluation System (NES). Vrouwen rapporteerden vaker bijwerkingen dan mannen, en in de totale populatie vonden we een klein doch significante stijging van vermoeidheid. Het effect was alleen aantoonbaar bij vrouwen en niet bij mannen. Personen die voor de eerste keer mefloquine gebruikten, hadden een hogere totaal score op de POMS, hetgeen correspondeert met een verslechtering van de stemming. Er waren geen aanwijzingen dat er concentratiestoornissen optraden tijdens de eerste drie weken van het gebruik van mefloquine.

In **Hoofdstuk 6.2** hebben we risicofactoren beschreven die de kans op neuropsychiatrische bijwerkingen kunnen vergroten tijdens de eerste drie weken van het gebruik van mefloquine. Het onderzoek wees uit dat het geslacht en de Body Mass Index -een maat voor overgewicht- belangrijke risicofactoren zijn. Stratificatie voor BMI liet zien dat de totaalscore van de POMS steeg bij vrouwen in de laagste BMI categorie, terwijl bij mannen geen effect van BMI zichtbaar was. De grootste stijging trad op bij vrouwen met een lage BMI die voor het eerst mefloquine gebruikten. Voorts vertoonden personen met een lage BMI een stijging in de reactietijd. Stratificatie voor geslacht en BMI liet zien dat deze stijging alleen voorkwam bij vrouwen met een lage BMI. Verdere stratificatie voor eerder gebruik van mefloquine liet zien dat de stijging alleen

aantoonbaar was bij vrouwen met een lage BMI die voor het eerst mefloquine gebruikten.

Het effect van BMI op het ontstaan van neuropsychiatrische klachten wees in de richting van een zogenaamde concentratie-effect relatie, die onderzocht werd en waarvan de resultaten beschreven zijn in **Hoofdstuk 6.3**. Onafhankelijk van het al dan niet optreden van neuropsychiatrische effecten, hadden vrouwen significant hogere serumspiegels van mefloquine dan mannen. Stratificatie voor BMI liet zien dat vrouwen met een lage BMI significant lagere serumspiegels hadden dan vrouwen met een hoge BMI. De serumspiegel van MMQ, de belangrijkste metaboliet van mefloquine was daarentegen verhoogd bij vrouwen met een lage BMI. De serumspiegel was significant hoger bij personen die wel dan bij personen die géén bijwerkingen ondervonden tijdens het gebruik van mefloquine. Er was geen relatie tussen het optreden van bijwerkingen en de spiegel van de metaboliet MMQ.

In de onderzoeken, die beschreven zijn in hoofdstuk 6, hebben we ons beperkt tot personen die uitsluitend mefloquine gebruikten en hebben we alle effecten van de reis uitgesloten. Derhalve blijft de mogelijkheid bestaan dat er verstoring van de resultaten optrad door de stress die een reis naar de tropen kan veroorzaken of door de eventuele leereffecten die de resultaten van de tweede test kunnen hebben beïnvloed. Daarom hebben we tevens een prospectief, dubbel blind, gerandomiseerd klinisch onderzoek uitgevoerd waarin personen ofwel Malarone (atovaquone+proguanil), ofwel mefloquine gebruikten. Dit onderzoek, dat in **Hoofdstuk 7** beschreven is, had als doel om het optreden van neuropsychiatrische klachten en concentratiestoornissen te vergelijken gedurende het profylactisch gebruik van mefloquine of Malarone. Wij vonden een significante verhoging van de frequentie van neuropsychiatrische klachten tijdens het gebruik van mefloquine, terwijl er op dit punt geen veranderingen optraden bij gebruikers van Malarone. Stratificatie voor duur van het verblijf in de tropen liet zien dat de grootste toename van de frequentie optrad bij de personen, die gedurende een korte tijd in de tropen verbleven. De conclusie van het onderzoek is dat Malarone op het punt van neuropsychiatrische effecten een veilig alternatief voor mefloquine is.

In **Hoofdstuk 8** beschrijven we de belangrijkste bevindingen. De onderzoeken naar het optreden van neuropsychiatrische klachten tijdens het profylactisch gebruik van mefloquine laten zien dat de frequentie waarmee deze

bijwerkingen optreden hoger is dan tijdens het gebruik van andere malariaprofylaxe en dat het vrouwelijk geslacht en een lage BMI de risicofactoren zijn, die de kans op deze klachten vergroten. Voorts bespreken we een aantal methodologische vraagstukken die inherent zijn aan het onderzoek naar neuropsychiatrische klachten tijdens het gebruik van mefloquine. Vervolgens bespreken we de klinische relevantie van onze bevindingen en doen we aanbevelingen voor verder onderzoek.

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About the author

Melanie Maria van Riemsdijk was born on May 26th, 1971 in Rotterdam, the Netherlands. She graduated in 1989 at the "Scholengemeenschap Gemini" in Ridderkerk. In the same year, she started her pharmacy study at the Utrecht University, in Utrecht, the Netherlands. During this period she participated in a research project at the Drug Safety Unit of the Inspectorate for Health Care (head: Prof. dr. B.H.Ch. Stricker) on psychiatric effects of antimalarials. She was trained to be a pharmacist and graduated in 1996. In 1996 she started the work described in this thesis at the Department of Epidemiology & Biostatistics (head: Prof. dr A. Hofman) of the Erasmus Medical Centre in Rotterdam. In 1999 she obtained a Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam. As of September 1st 2000 she started working as a pharmaco-epidemiologist at the Scientific Institute for Dutch Pharmacists.