Mefloquine Increases the Risk of Serious Psychiatric Events During Travel Abroad: A Nationwide Case-Control Study in the Netherlands

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Background: Psychiatric events during travel abroad account for a large percentage of medical repatriations arranged by insurance companies. Several risk factors have been proposed for such events, one of these being use of mefloquine. We investigated the risk of psychiatric events during use of mefloquine.

Method: We performed a nationwide case control study using medical records from 4 large alarm centers in the Netherlands. Cases were patients contacting the alarm centers because of psychiatric events, according to International Code Primary Care code P (all psychiatric symptoms) or *International Classification of Diseases*, Ninth Edition, codes 290–319 (all psychiatric syndromes). To every case we matched up to 6 controls by alarm center, calendar time, and continent of travel. All controls had contacted the alarm centers because of nonpsychiatric medical reasons. Shortly after the anticipated day of return, cases and controls received a questionnaire regarding travel characteristics, gender, age, marital status, education, weight, height, general health, history of psychiatric diseases, use of medicines, smoking status, alcohol intake, coffee intake, and use of malaria prophylaxis. Dates of travel for the source population were between September 1, 1997, and June 1, 2000.

Results: The study population consisted of 111 cases and 453 controls. The risk of psychiatric events during the use of mefloquine was 3.5 (95% CI = 1.4 to 8.7). In females, the risk was strongly increased, with an odds ratio of 47.1 (95% CI = 3.8 to 578.6). Stratification for history of psychiatric diseases showed that the risk of psychiatric events during use of mefloquine in cases without a history of psychiatric diseases was 3.8 (95% CI = 1.4 to 10.1), whereas the risk in cases with a history of psychiatric diseases was 8.0 (95% CI = 1.8 to 35.8).

Conclusion: The use of mefloquine is associated with an increased risk of psychiatric events in females and in patients with a history of psychiatric diseases.

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Psychiatric syndromes during travel abroad account for a large percentage of medical repatriations arranged by insurance-based medical alarm centers.[1] Several risk factors for psychiatric syndromes during travel have been proposed. These risk factors include travel destination, traveling 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.[4–10] Factors influencing tolerability of mefloquine are still largely unknown, although it has been demonstrated that 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 to assess the risk of psychiatric events during the use of malaria prophylaxis while traveling abroad.

METHOD

Setting

This study was performed with medical data from the 4 largest Dutch alarm centers: ANWB (Dutch Motorists Association), The Hague; Elvia Assistance, Amsterdam; SOS International, Amsterdam; and Eurocross, Noordwijk, the Netherlands. The alarm centers are associated with insurance companies that provide travel insurances. Insured travelers can contact the alarm centers in case of serious medical problems. Every traveler seeking medical help while traveling or staying abroad has to contact the alarm

center to assure that medical help abroad is reimbursed. If necessary, a team of specialized 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 Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, the Netherlands, and written informed consent was obtained from all responding participants.

Source Population

The source population consisted of all persons, aged 15 years or older, who contacted 1 of the 4 alarm centers for any medical reason while traveling outside Europe between September 1, 1997, and June 1, 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 an alarm center for psychiatric disturbances during travel. Cases were identified through the automated database, which contains information on medical complaints coded by either International Code Primary Care (ICPC) code P (all psychiatric symptoms) or *International Classification of Diseases,* Ninth Edition, (ICD-9) codes 290–319 (all psychiatric syndromes). The date of first contact was defined as the index date.

Six controls per each case were selected at random from the source population of persons contacting the alarm centers for nonpsychiatric but otherwise medical reasons at the time the case occurred. Controls were matched to the cases by alarm center, calendar time (± 14 days), and continent of travel.

Data Collection

Data were collected by means of a self-administered questionnaire (available in Dutch by request), which was sent directly to both cases and controls after the anticipated day of return. The questionnaire was accompanied by a cover letter in which the research hypothesis was formulated in general terms without specific reference to psychiatric events. A reminder was sent to all nonresponders 1 month later. The questionnaire contained closed-ended questions regarding travel characteristics, gender, age, marital status, education, weight, height, general health, history of psychiatric diseases, use of medicines, smoking status, alcohol intake, coffee intake, and use of malaria prophylaxis. We incorporated the validated Dutch Symptom Checklist (SCL-90)[13,14] for validation of the psychiatric status. The SCL-90 is a self-report clinical rating scale oriented toward the symptomatic behavior 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 5-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]

Exposure Assessment

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

Analysis

Univariate comparisons between cases and controls were conducted with Student t tests in case of normally distributed continuous variables. Crude odds ratios and 95% confidence intervals for the use of mefloquine, proguanil, or other malaria prophylaxis as compared to nonuse were calculated. Adjusted odds ratios were calculated by multivariate conditional logistic regression analysis after adjustment for potential confounders such as age, gender, BMI or body weight, traveling alone, and history of psychiatric diseases, which were univariately associated with psychiatric events. Missing values were incorporated into the analyses using the missing indicator method.[15]

We conducted 3 sensitivity analyses to examine whether our case or control definition was misclassified. On the basis of the total score on the SCL-90, cases were retained only if they had a clinically relevant score on the SCL-90 and controls only if they had a normal score on the SCL-90 according to either of the specific cutoff values of the case. For the 3 analyses, we used the following respective cutoff points: for males, 116, 124, and 131; for females, 130, 139, and 149. These cutoff points have been validated in the Dutch population.[14]

Unconditional logistic regression analyses were performed in order to stratify for potential effect modification by history of psychiatric diseases. Statistical interaction was defined as a departure from additivity of effects, and interaction of factors A and B was present if $(OR_{A+B+} - OR_{A+B-}) - (OR_{A-B+} - 1) > 0$.[16,17] Two-tailed p values less than .05 were considered statistically significant.

RESULTS

From September 1, 1997, until June 1, 2000, 185 cases of psychiatric disturbance were identified, and to those cases, 1017 controls (1.0:5.5) were matched. A total of 800 (66.6%) questionnaires were received (116 cases and 684 controls). Nonresponders were significantly younger than responders (41 years vs. 46 years, $p < .001$), and more females responded than males (70.0% vs. 67.2%, $p = .005$). The response was slightly lower in cases (63.0%) than in

Table 1. General Characteristics of the Study Population: Persons Who Contacted the Alarm Center for Psychiatric Disturbances (cases) or Nonpsychiatric Medical Reasons (controls) During Travel Abroad

Characteristic	Cases (N = 111)	Controls (N = 453)	Conditional OR (95% CI) or p Value
Male, N (%)	36 (32.4)	214 (47.2)	Reference
Female, N (%)	75 (67.6)	239 (52.8)	2.1 (1.3 to 3.4)[a]
Age, mean (SD), y	38.9 (14.9)	46.7 (18.5)	.001[a]
Body mass index, mean (SD)[b]	22.8 (2.9)	24.4 (4.0)	.003[a]
< 20, N (%)	16 (14.4)	39 (8.6)	Reference
20–25, N (%)	43 (38.7)	197 (43.5)	0.5 (0.2 to 1.0)
> 25, N (%)	22 (19.8)	148 (32.7)	0.3 (0.1 to 0.7)[a]
Education, N (%)[b]			
Primary (vocational)	13 (11.7)	71 (15.7)	Reference
Secondary (vocational)	43 (38.7)	155 (34.2)	1.5 (0.7 to 3.0)
College/university	29 (26.1)	160 (35.3)	1.0 (0.5 to 2.0)
Marital status, N (%)[b]			
Unmarried/divorced	36 (32.4)	222 (49.0)	Reference
Married/living together	44 (39.6)	131 (28.9)	1.9 (1.2 to 3.0)[a]
Widow/widower	4 (3.6)	32 (7.1)	0.8 (0.3 to 2.5)
Traveling alone, N (%)[b]			
No	54 (48.6)	306 (67.5)	Reference
Yes	31 (27.9)	83 (18.3)	2.1 (1.2 to 3.6)[a]
Medical complaints, N (%)[b]			
No	22 (19.8)	139 (30.7)	Reference
Yes	62 (55.9)	240 (53.0)	1.6 (0.9 to 2.7)
History of psychiatric disease, N (%)[b]			
No	28 (25.2)	293 (64.7)	Reference
Yes	55 (49.5)	79 (17.4)	7.0 (4.0 to 12.1)[a]
Use of medication, N (%)[b]			
No	31 (27.9)	163 (36.0)	Reference
Yes	52 (46.8)	213 (47.0)	1.3 (0.8 to 2.2)
Prophylaxis with antimalarial drugs, N (%)			
No	71 (64.0)	345 (76.2)	Reference
Yes	36 (32.4)	100 (22.1)	2.1 (1.1 to 3.8)[a]
Unknown	4 (3.6)	8 (1.8)	2.4 (0.6 to 9.2)
Alcohol intake, N (%)[b]			
None	22 (19.8)	93 (20.5)	Reference
< 1 unit daily	50 (45.0)	185 (40.8)	1.0 (0.5 to 2.1)
1–5 units daily	9 (8.1)	106 (23.4)	0.3 (0.1 to 0.8)[a]
> 5 units daily	1 (0.9)	2 (0.4)	2.3 (0.2 to 27.3)
Coffee intake, N (%)[b]			
None	15 (13.5)	76 (16.8)	Reference
1–4 cups per day	49 (44.1)	209 (46.1)	1.3 (0.7 to 2.5)
5–9 cups per day	16 (14.4)	84 (18.5)	1.1 (0.5 to 2.4)
≥ 10 cups per day	1 (0.9	11 (2.4)	0.5 (0.1 to 4.4)
Smoking status, N (%)[b]			
No	49 (44.1)	264 (58.3)	Reference
Yes	34 (30.6)	118 (26.0)	1.5 (0.9 to 2.5)
Neuropsychiatric event, N (%)			
Depression	17 (15.3)		
Anxiety/panic attack	16 (14.4)		
Psychosis	14 (12.6)		
Insomnia	18 (16.2)		
Drowsiness/collapse	7 (6.3)		
Hallucinations	2 (1.8)		
Agitation	2 (1.8)		
Manic reaction	2 (1.8)		
Disorientation	2 (1.8)		
Lethargy	3 (2.7)		
Not specified	28 (25.2)		

[a]Statistically significant at < .05.
[b]Subset Ns do not add up to total N because of missing values.

controls (67.0%), but this difference was not significant. Five cases and 231 controls had to be excluded from the conditional logistic regression analyses because they had no responding control or case, respectively, 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, marital status, traveling alone, prophylactic use of antimalarial drugs, and history of psychiatric disease were associated with an increased risk, whereas age, a high BMI, and moderate use of alcohol were associated with a decreased risk of psychiatric events abroad. The most frequent psychiatric events were depression, anxiety, psychosis, and insomnia, but in 28 cases the precise diagnosis was unknown. Fifty-eight (52.2%) of the 111 cases returned home earlier and 3 cases (2.7%) returned home later than planned because of the psychiatric events. Others were treated mostly through local medical assistance by switching to another antimalarial agent or with psychotropic medication.

Regarding 4 cases and 8 controls, the status of malaria prophylaxis was unknown. Table 2 shows that the adjusted risk of psychiatric events during use of mefloquine was 3.5 (95% CI = 1.4 to 8.7), whereas there was no significant association with proguanil. 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 effect of mefloquine on the occurrence of psychiatric events was most pronounced among females (OR = 47.1 [95% CI = 3.8 to 578.6]), whereas the risk was not significantly elevated for males. Mefloquine use elevated the risk of psychiatric events both in persons with (OR = 8.0 [95% CI = 1.8 to 35.8]) and without (OR = 3.8 [95% CI = 1.4 to 10.1]) a history of psychiatric disease. The relative excess risk due to interaction was 35.1 (95% CI = –68.7 to 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 3). The adjusted results for BMI and body weight were similar, and only those for BMI are given. Although BMI may be both a confounder and an effect modifier, we were not able to explore the potential interaction between gender and BMI because of low numbers in the strata.

We conducted 3 sensitivity analyses with respect to the case-control definition by using the total score on the SCL-90. By varying the cutoff points for the case definition, the odds ratio for

Table 2. Association Between Use of Malaria Prophylaxis and the Occurrence of Psychiatric Events During Travel Abroad[a]

	Cases (N = 107)		Controls (N = 445)		Crude Odds Ratio	Adjusted Odds Ratio
Population	N	%	N	%	(95% CI)	(95% CI)
Total						
No prophylaxis	71	66.4	345	77.5	Reference	Reference[b]
Proguanil	10	9.3	34	7.6	2.1 (0.9 to 5.1)	1.3 (0.5 to 3.8)
Mefloquine	22	20.6	41	9.2	3.2 (1.5 to 7.0)	3.5 (1.4 to 8.7)
Other	4	3.7	25	5.6	0.9 (0.3 to 2.9)	0.7 (0.2 to 2.6)
Male						
No prophylaxis	25	71.4	162	76.8	Reference	Reference[c]
Proguanil	3	8.6	11	5.2	1.3 (0.3 to 5.6)	1.3 (0.2 to 8.6)
Mefloquine	6	17.1	24	11.4	1.6 (0.5 to 5.4)	2.5 (0.5 to 12.1)
Other	1	2.9	14	6.6	0.7 (0.1 to 7.4)	0.3 (0.1 to 5.8)
Female						
No prophylaxis	46	63.9	183	78.2	Reference	Reference[c]
Proguanil	7	9.7	23	9.8	1.4 (0.3 to 5.7)	1.2 (0.2 to 8.5)
Mefloquine	16	22.2	17	7.3	10.0 (1.9 to 51.8)	47.1 (3.8 to 578.6)
Other	3	4.2	11	4.7	0.9 (0.1 to 10.3)	1.3 (0.1 to 20.3)

[a]Four cases and 8 controls excluded because it was unknown whether they had used antimalarials.
[b]Odds ratio adjusted for gender, age, body mass index, traveling alone, and history of psychiatric diseases.
[c]Odds ratio adjusted for age, body mass index, traveling alone, and history of psychiatric diseases.

Table 3. Estimation of Interaction and Relative Excess Risk Due to Interaction Between Exposure to Mefloquine/History of Psychiatric Disease and Occurrence of Psychiatric Events During Travel Abroad[a]

	Cases		Controls		Odds Ratio
Population	N	%	N	%	(95% CI)[b]
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 to 10.6)
Exposed/no history of psychiatric disease	8	11.3	33	10.2	4.9 (1.3 to 18.5)
Exposed/history of psychiatric disease[c]	11	15.5	3	0.9	43.6 (4.4 to 434.4)

[a]In patients for whom there were complete data.
[b]Odds ratio adjusted for age, gender, body mass index, and traveling alone.
[c]Relative excess risk due to interaction: (43.6 – 4.6 – 4.9 + 1) = 35.1 (95% CI = –68.7 to 138.9). Proportion of cases attributable to the interaction of use of mefloquine and history of psychiatric disease: 35.1/43.6 = 0.81.

psychiatric events during use of mefloquine increased from 2.0 (95% CI = 0.7 to 5.7) for the lowest, via 3.1 (95% CI = 1.0 to 10.0) for the middle, to 6.1 (95% CI = 1.5 to 25.2) for the highest cutoff point.

DISCUSSION

This study demonstrates that use of mefloquine is associated with an increased risk of psychiatric events during travel. This risk was strongly increased in women but only slightly and nonsignificantly in males. That women are more susceptible than men has been brought forward by several authors.[18–20] Recently, we confirmed this female preponderance in a prospective double-blind study in which the occurrence of neuropsychiatric effects during use of atovaquone plus proguanil was compared to that during mefloquine use.[21,22] Despite the fact that mefloquine is contraindicated in persons with a history of psychiatric diseases,[23] 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 8-fold as compared to nonuse.

Mefloquine has acetylcholinesterase-inhibiting properties, and stereospecific inhibition of acetylcholinesterase has been reported.[24,25] 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.[26] Hence, the adverse reaction profile of mefloquine is compatible with its pharmacologic activity.

In our study, a high BMI was protective. One explanation for this effect 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.[27] 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.[27] 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 tissue. This effect is reminiscent of the principle that overweight persons require more anesthetic to induce anesthesia but have a prolonged recovery phase because the anesthetic agent is slowly released from adipose tissues.

An epidemiologic field study such as ours may be limited by selection bias, information bias, or confounding. Selection bias might occur whenever the inclusion of cases and controls is in some way associated with the exposure of interest. This bias seems unlikely, as almost 70% of the source population participated, and nonresponse did not differ between cases and controls. Information bias might have occurred if patients with psychiatric events had a better recall of drug use than patients with nonpsychiatric events. For 2 reasons, we think that this potential recall bias is unlikely. Firstly, our controls also experienced a serious and often frightening medical event. Hence, any recall bias might be expected to occur in cases and controls alike. That this bias did not occur is confirmed by the fact that the overall drug use in cases and controls was the same. Secondly, our cover letter and questionnaire alluded to the study as an investigation of the Inspectorate for Health Care on the health of travelers and the quality of repatriation in very general terms. The emphasis was on the event that happened while traveling abroad and the way it was handled, but nothing in the letter pointed to a special interest in psychiatric events or antimalarial drugs.

Misclassification of the outcome of interest may be another potential form of information bias. Substantial misclassification, however, seems unlikely as cases were all persons who contacted the alarm center for psychiatric symptoms while traveling abroad, and it must be highly unusual for people who contact the alarm center because of psychiatric symptoms to not have psychiatric disturbances. On the other hand, we can not exclude that the type of psychiatric syndrome was misclassified, because most patients did not visit a psychiatrist while traveling abroad. Under such circumstances, a psychiatric differential diagnosis may be difficult to make. For this reason and because mefloquine has been associated with a wide variety of neuropsychiatric events, 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 to 25.2). Hence, application of the most stringent criteria increased rather than decreased the magnitude of the association.

Some authors have suggested that physiologic and psychological stress of intercontinental travel may confound the association between mefloquine and neuropsychiatric adverse events.[6,7,28] Relocation, mode of transportation, travel destination, traveling alone, and time zone changes are recognized stressors.[1–3,29,30] Also, being away from home in an unfamiliar and uncontrollable environment means that some travelers may be exposed to considerable stress at a time of maximal vulnerability.

In this study, we tried to control for the effects of travel by matching for continent to which the cases traveled. All subjects went to destinations outside Europe, were transported by air, and encountered the same time zone changes. Furthermore, by matching for continent, we reduced to some extent the confounding effects of extreme experiences, for example, exposure to violent criminal activities, which may differ by 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 traveling alone, the use of mefloquine adds substantially to mental disturbances during travel. These effects were mainly observed in women. Despite the fact that mefloquine is contraindicated in persons with a history of psychiatric diseases, a substantial number of users of mefloquine had such a history. Since persons with a positive history of psychiatric diseases have a strong risk of relapse with mefloquine use, other antimalarial drugs should be prescribed to such individuals.

Drug names: atovaquone (Mepron), atovaquone and proguanil (Malarone), chloroquine (Aralen and others), mefloquine (Lariam and others).

REFERENCES

1. Monden MA, Meester WJ. Psychische decompensatie tijdens vakantie in het buitenland [Mental decompensation during vacation abroad]. Ned Tijdschr Geneeskd 1994;138:1520–1523
2. Sauteraud A, Hajjar M. Troubles psychotiques: frequence plus elevee lors des voyages en Asie [Psychotic disorders: higher incidence during travels in Asia]. Presse Med 1992;21:805–810
3. Jauhar P, Weller MP. Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. Br J Psychiatry 1982;140: 231–235
4. Weinke T, Trautmann M, Held T, et al. Neuropsychiatric side effects after the use of mefloquine. Am J Trop Med Hyg 1991;45:86–91
5. Steffen R, Fuchs E, Schildknecht J, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa. Lancet 1993;341:1299–1303
6. Schlagenhauf P, Steffen R, Lobel H, et al. Mefloquine tolerability during chemoprophylaxis: focus on adverse event assessments, stereochemistry and compliance. Trop Med Int Health 1996;1:485–494
7. Schlagenhauf P, Lobel H, Steffen R, et al. Tolerance of mefloquine by SwissAir trainee pilots. Am J Trop Med Hyg 1997;56:235–240
8. Boudreau E, Schuster B, Sanchez J, et al. Tolerability of prophylactic Lariam regimens. Trop Med Parasitol 1993;44:257–265
9. Croft A, Garner P. Mefloquine to prevent malaria: a systematic review of trials. BMJ 1997;315:1412–1416
10. Lobel HO, Miani M, Eng T, et al. Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993;341:848–851
11. van Riemsdijk MM, Sturkenboom MCJM, Ditters JM, et al. Risk factors for neuropsychiatric adverse events and concentration impairment during the prophylactic use of mefloquine. In: Neuropsychiatric Effects of Anti-

malarial Drugs [thesis]. Rotterdam, the Netherlands: Erasmus University Rotterdam; 2001
12. van Riemsdijk MM, van der Klauw MM, van Heest JA, et al. Neuropsychiatric effects of antimalarials. Eur J Clin Pharmacol 1997;52:1–6
13. Arrindell WA, Ettema H. Dimensionele structuur, betrouwbaarheid en validiteit van de Nederlandse berwerking van de Symptom Checklist (SCL-90); gegevens gebaseerd op een fobische en een 'normale' populatie. Ned Tijdschr Psychol 1981;36:77–108
14. Koeter MWJ, Ormel J, van den Brink W. Totaalscore op de SCL-90 als maat voor de ernst van de psychopathologie. Ned Tijdschr Psychol 1988; 43:381–391
15. Huberman M, Langholz B. Application of the missing indicator method in matched case-control studies with incomplete data. Am J Epidemiol 1999;150:1340–1345
16. Hosmer D, Lemeshow S. Confidence interval estimation of interaction. Epidemiology 1992;3:452–456
17. Rothman K. Modern Epidemiology. Boston, Mass: Little, Brown; 1986
18. Philips M. Adverse events associated with mefloquine: women may be more susceptible to adverse events [letter]. BMJ 1996;313:1552–1553
19. Schwartz E, Potasman I, Rotenberg M, et al. Serious adverse events of mefloquine in relation to blood level and gender. Am J Trop Med Hyg 2001;65:189–192
20. van Riemsdijk MM, Ditters JM, Sturkenboom MC, et al. Neuropsychiatric events during prophylactic use of mefloquine before travelling. Eur J Clin Pharmacol 2002;58:441–445
21. van Riemsdijk MM, Sturkenboom MC, Ditters JM, et al. Atovaquone plus proguanil versus mefloquine for malaria prophylaxis: a focus on neuropsychiatric adverse events. Clin Pharmacol Ther 2002;72:294–301
22. Overbosch D, Schilthuis H, Bienzle U, et al, and the Malarone International Study Team. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travellers: results from a randomized double-blind study. Clin Infect Dis 2001;33:1015–1021
23. Landelijk Coördinatiecentrum R. Malariaprofylaxebulletin 1999. Augustus 1999
24. Lim LY, Go ML. The anticholinesterase activity of mefloquine. Clin Exp Pharmacol Physiol 1985;12:527–531
25. Ngiam TL, Go ML. Stereospecific inhibition of cholinesterases by mefloquine enantiomers. Chem Pharm Bull (Tokyo) 1987;35:409–412
26. Hoover DB. Cholinesterases and cholinesterase inhibitors. In: Craig CR, Stitzel RE, eds. Modern Pharmacology. 4th ed. Boston, Mass: Little, Brown; 1994:161–168
27. Gram TE. Drug absorption and distribution. In: Craig CR, Stitzel RE, eds. Modern Pharmacology. 4th ed. Boston, Mass: Little, Brown; 1994:19–32
28. Davis TM, Dembo LG, Kaye-Eddie SA, et al. Neurological, cardiovascular and metabolic effects of mefloquine in healthy volunteers: a double-blind, placebo-controlled trial. Br J Clin Pharmacol 1996; 42:415–421
29. Lucas G. Psychological aspects of travel. Travel Med Int 1990;8:99–104
30. McIntosh I. The stress of modern travel. Travel Med Int 1990;8:118–121