ADVERSE REACTION TO MEFLOQUINE ASSOCIATED WITH ETHANOL INGESTION

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Abstract • Résumé

A 40-year-old man with no history of neuropsychiatric illness was taking one 250-mg tablet of mefloquine (MFQ) weekly for malaria prophylaxis while in Tanzania. He experienced no adverse reaction in association with his first two doses. Concurrently with both his third and his fourth dose he consumed about half a litre of whisky. On both occasions he experienced hallucinations, paranoid delusions and suicidal ideation. Thereafter he continued taking the MFQ, abstained completely from ethanol ingestion and had no recurrence of psychiatric symptoms. It is hypothesized that the combination of MFQ and ethanol caused the two episodes of severe psychiatric disturbance.

Un homme de 40 ans sans antécédents de maladie neuropsychiatrique prenait un comprimé de 250 mg de méfloquine (MFQ) par semaine comme prophylaxie antipaludéenne pendant son séjour en Tanzanie. Les deux premières doses ne lui ont causé aucune réaction défavorable. En même temps que ses troisième et quatrième doses, il a consommé environ un demi-litre de whisky. Dans les deux cas, il a été en proie à des hallucinations, à un délire paranoïde et à des tendances suicidaires. Par la suite, il a continué de prendre de la MFQ, a évité toute consommation d'éthanol et les symptômes psychiatriques ne sont pas réapparus. On suppose que la combinaison de MFQ et d'éthanol a causé les deux crises de troubles psychiatriques graves.

Mefloquine (MFQ) is at present the drug of choice in Canada[1] and the United States[2] for the chemoprophylaxis of chloroquine-resistant *Plasmodium falciparum* malaria. On rare occasions it has been associated with severe neuropsychiatric adverse drug reactions.[3–10] The overall incidence of such drug reactions has been estimated at one to five episodes per 10 000 patients given MFQ prophylaxis.[3] The most pertinent studies that have addressed this estimate are the following. In 1990, by means of passive surveillance, 23 cases of psychiatric disturbance (mostly restlessness, anxiety, acute depression and acute psychosis) were reported among approximately 1.2 million people worldwide who had taken MFQ prophylactically.[7] According to an updated review of passive surveillance of adverse reactions to MFQ published in 1992,[8] 32 serious psychiatric episodes (12 depressive and 20 psychotic) were reported among an estimated 1.7 to 2.5 million people who had taken MFQ prophylactically. Although the incidence of severe psychiatric drug reactions was not calculated, if one takes 2.1 million patients (the midpoint of the estimate) as the denominator, the incidence would be 0.0015%, or roughly 1 per 66 000 people who take MFQ prophylactically. In Canada, on the basis of semiactive surveillance undertaken when MFQ was distributed under an open investigational new drug (IND) protocol before its licensure, one case of psychotic depression was reported among an estimated 21 620 people who took MFQ prophylactically.[11] Finally, in retrospective reporting of adverse drug reactions to antimalarial drugs by means of a questionnaire given to European travellers returning home from malarial areas, one episode of depression was reported among 3386 travellers who had taken MFQ either alone or in combination with other drugs; it was considered unlikely that this episode was causally related to MFQ.[9]

We report here an episode of acute psychosis and depression in association with the combination of MFQ and ethyl alcohol, an association not previously reported.

CASE REPORT

A 40-year-old male geologist (Y) in excellent health with no history of seizures or psychiatric problems or any other significant medical problems began taking one 250-mg tablet of MFQ every Sunday morning, beginning 1 week before his departure for an 8-week stay in rural Tanzania. He was taking no other medications. While in Tan-

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zania he shared a tent with a fellow geologist (Z), who was taking no antimalarial drugs. The two men had shared the tent at the same site on previous occasions before Y started taking MFQ. On the night before he was due to take his third weekly dose of MFQ, Y shared with Z a 1.2-L bottle of a brand-name whisky. Each man ingested about half the bottle. The next day, before taking his third dose as usual in the morning, Y experienced auditory and visual hallucinations. He had paranoid delusions that Z was trying to kill him, such that he felt tempted to murder Z in self-defence. Fortunately, Y was able to restrain himself; moreover, he took his third dose of MFQ. During the following 24 hours Y felt acutely depressed and suicidal but was again able to refrain from causing harm. By Tuesday morning he felt perfectly fine and resumed work. His colleague Z had experienced no such reactions.

The following Saturday night the two men again shared a 1.2-L bottle of the same brand of whisky, purchased at a different store, and Y took his weekly MFQ tablet the next morning. Over a 36-hour period, beginning the night before he took his MFQ tablet, Y experienced the same symptoms as he had the previous week, while Z remained free of psychiatric symptoms. Thereafter, until he was seen at the Infectious Diseases Clinic of the Ottawa Civic Hospital 6 weeks later, Y abstained completely from alcohol, continued taking his MFQ weekly and had no further psychiatric disturbance.

Y had often ingested similar amounts of alcohol in the past, either in the absence of any medications or else while taking a combination of chloroquine and proguanil, with no consequent symptoms (including depressive symptoms or hallucinations). Generally, his pattern of alcohol consumption had been to drink heavily on Saturday nights and to either abstain or else drink very little during the rest of the week. He had no history of illicit drug use. He reported that two siblings were epileptic. When Y was examined in the clinic his mental status was found to be normal, and he had no signs of alcohol-related liver disease or any other abnormal physical findings. His liver function tests and complete blood count were normal, and the result of a malaria smear was negative.

Comments

The circumstances of this case strongly suggest that it was the combination of MFQ and ethanol that caused Y's two episodes of severe psychiatric disturbance. Had they been attributable to toxic substances in the whisky, Z should have been affected. Had they been attributable to the effects of alcohol on Y, on Y in that particular setting, or on Y in that setting taking other antimalarial drugs, then Y should have been affected previously. Had they been attributable to the effects of MFQ alone on Y, then he should have been affected subsequently, particularly in view of the drug's long elimination half-life (2 to 4 weeks).[3,12]

It is interesting to compare this case with the 32 cases of severe psychiatric adverse drug reactions reported by Bem, Kerr and Stuerchler.[8] Among the 20 people who experienced psychotic episodes, a mean of four tablets had been taken at the onset of symptoms; ethanol abuse was suspected in 1 patient who was also taking chloroquine, but no further details of the ethanol ingestion were provided. Among the 12 people who experienced severe depression, a mean of three tablets had been taken at the onset of symptoms; 3 patients had no history of psychiatric illness and were taking no other medications (as was true of the patient reported here), and each of those 3 attempted suicide. Six patients continued taking MFQ, with a subsequent increase in intensity of symptoms; by contrast, the patient reported here had no symptoms concurrently with continued MFQ ingestion once he began abstaining from ethanol.

One can only speculate as to the reasons why this combination caused Y's psychiatric episodes. The first possibility is that sudden, substantial ethanol ingestion somehow led to higher MFQ concentrations in the central nervous system (CNS), either by interfering with MFQ metabolism or, more likely, by increasing the distribution of MFQ into the CNS. The incidence of neuropsychiatric adverse reactions to MFQ is clearly related to the dose, the regimen and the resulting plasma concentration. When used for treatment of malaria at a dose generally 1.0 to 1.25 g higher than that used for prophylaxis, the risk of neuropsychiatric drug reactions is 60 times greater than that observed with MFQ prophylaxis.[10] Even when administered for prophylaxis, when a regimen consisting of an initial loading dose of 250 mg daily for 3 days followed by 250 mg weekly was compared with the standard regimen of 250 mg weekly, the incidence of neurologic symptoms increased significantly during the first week among the volunteers who took the loading dose, but no difference was seen between the two groups during weeks 8 to 11 (when the study was terminated). Also, in parallel, the mean MFQ plasma levels were significantly higher in the loading-dose group at 72 hours, but were nearly identical in the two groups at 11 weeks.[13]

A second possibility is that these episodes represented acute alcoholic psychosis. If so, one must explain why this patient had never experienced such symptoms before, after ingesting a similar quantity of ethanol. In the rat, MFQ inhibits three oxidative hepatic microsomal enzymes and may therefore be capable of interfering with the oxidative detoxification of concurrently administered drugs (Hoffmann–La Roche: unpublished data, 1990). MFQ might therefore inhibit hepatic metabolism of ethanol, leading to higher blood ethanol levels than would otherwise occur were the same quantity of ethanol ingested.

Third, ethanol may potentiate MFQ neurotoxicity by lowering the brain threshold for toxicity. In this regard it may be relevant that related quinolones have been shown to inhibit the receptor-binding capacity of gamma aminobutyric acid (GABA), an important inhibitory neurotransmitter;[14] deficits in GABA have been identified in some patients with psychotic depression.[15]

Animal pharmacokinetic studies of MFQ distribution into the CNS, with and without comcomitant ethanol, might help to discriminate between these three possibilities. Such studies should also examine the effects of MFQ and ethanol on neurotransmitters such as GABA. Similar human studies would likely be difficult to perform, but it would be interesting to examine the concentration of MFQ and metabolites in cerebrospinal fluid (CSF), for example when a lumbar puncture is performed in the diagnostic investigation of a patient taking MFQ with suspected cerebral malaria; if such an investigation were done, an attempt should be made to relate CSF MFQ concentrations to both plasma MFQ concentrations and to the antecedent regimen of oral MFQ administration. In the meantime, whatever the mechanism of adverse reactions to MFQ, it may be prudent to warn patients taking MFQ prophylactically to avoid excessive ethanol intake while taking the drug and for several weeks thereafter, given its long elimination half-life. There is no evidence that absolute abstention is necessary.

From this single case report one cannot assess how best to treat a patient who presents with acute psychosis secondary to concurrent MFQ and ethanol ingestion, but standard treatment with phenothiazines or benzodiazepines, or both, as for any acute psychosis, would seem to be appropriate.

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