

Short Report

Problems in the therapy of mixed malarial infections: a case of infection with *Plasmodium falciparum* and *P. malariae* treated with mefloquine and halofantrine

F. J. Hess, H. D. A. Kilian, H. D. Nothdurft and T. Löscher *Department of Tropical Medicine and Infectious Diseases, University of Munich, Munich, Germany*

Mixed malarial infections of *Plasmodium falciparum* and *P. malariae* are not uncommon but they may often be overlooked because there is a tendency for *P. falciparum* to predominate and the parasitaemia with *P. malariae* is usually very low.

Therapy of cases of mixed infections with *P. falciparum* and *P. malariae*, *P. vivax* or *P. ovale* should clearly be aimed at *P. falciparum* as the potentially lethal infectious agent (COOK, 1988), followed by a course of primaquine in the case of *P. vivax* or *P. ovale*. For non-immune subjects, mefloquine and halofantrine are the currently recommended first line drugs for uncomplicated falciparum malaria imported from African countries where chloroquine resistance is common (WHO, 1992).

However, very limited information is available concerning the efficacy of these 2 drugs in the treatment of quartan malaria. DIXON and co-workers (1983) have successfully used mefloquine to treat a case of *P. malariae* and they reported rather slow resolution of fever and parasitaemia. Similarly, WEINKE *et al.* (1993) reported the successful treatment of 2 cases of *P. malariae* infection (one mixed with *P. falciparum*) with halofantrine, but in both reports the follow-up period was only 28 d.

Here we report a patient with a mixed infection of *P. falciparum* and *P. malariae* treated initially with mefloquine and subsequently with halofantrine; the possible failure of both drugs is discussed.

In July 1991 a 46 years old German woman presented at a peripheral hospital in Germany with fever (39.2°C), chills, headache and anorexia of 3 d duration, 12 d after returning from 2 weeks' holiday in Kenya. She denied having taken any malaria chemoprophylaxis or anti-malarial treatment. The diagnosis of falciparum malaria was made by examination of blood films which had been sent to our institute for confirmation. The initial parasitaemia was 3% (136 000/μL). Other than a thrombocytopenia of 128 000/μL there was no abnormality or sign of complicated malaria. Consequently she was treated with mefloquine in a total dose of 1500 mg (750 mg followed by 500 mg 6 h later and 250 mg after a further 12 h), equivalent to 20 mg/kg body weight. She did not vomit after taking the drug. Fever had disappeared by day 4 and parasitaemia by day 6. The patient was discharged on day 7, clinically fully recovered.

In October 1991 (78 d later) the patient presented again at the same hospital with fever (40°C), shivering and chills. She had not been abroad since her last hospital admission. Suspecting a *P. falciparum* recrudescence, treatment with halofantrine was started immediately. However, all blood slides sent to us clearly revealed a *P. malariae* mono-infection. She was given 3 doses of halofantrine, 500 mg, orally at intervals of 6 h. Again there was no vomiting and recovery was uneventful. Clearance of fever and parasitaemia occurred at days 3 and 4 respectively. Treatment was repeated one week after the initial course, using the same dose of halofantrine.

In January 1992 (106 d after her first admission) the patient presented a third time at the same hospital with

fever and headache. Again *P. malariae* was detected in thick and thin blood films sent to us, although she had not travelled to a malaria endemic area since her last admission. Apart from mild splenomegaly no other abnormality could be found and again she was treated with 2 full courses of halofantrine with an interval of one week. Her fever and parasitaemia cleared by days 2 and 8 respectively. After this third treatment the patient was finally referred to us for further counselling and was advised to consult us directly in case of further symptoms. To date (March 1993, 410 d after her last therapy) she is in good health, no further episode of fever attributable to malarial infection has occurred, and repeated blood films have always been negative for *Plasmodium*.

In this patient we observed a recrudescence of *P. malariae* infection more than 2 months after mefloquine treatment. There can be no doubt that the drug was sufficiently absorbed, since concomitant infection with *P. falciparum* was cleared promptly. Therefore one might conclude that mefloquine failed to eradicate a very low parasitaemia of *P. malariae*, which had been overlooked at the initial examination. Alternatively it is possible that *P. malariae* parasites were not present in peripheral blood initially, due to a longer incubation period, and, when parasitaemia developed later, the plasma level of mefloquine was no longer sufficient to clear the infection completely.

In the case of halofantrine, on the other hand, poor absorption resulting in low plasma concentrations may have caused the first therapy failure even though a second course was administered after one week, which in falciparum malaria is thought to have almost 100% efficacy in non-immune subjects (NOTHDURFT *et al.*, 1993). This explanation appears to be more likely than true halofantrine resistance. Such a view is also supported by the fact that the second treatment with halofantrine has obviously resulted in complete cure. Nevertheless, it cannot be ruled out completely that the plasma level of halofantrine needed for effective treatment of *P. malariae* is higher than that for *P. falciparum*.

Interestingly, both clinical episodes of *P. malariae* mono-infection in our patient occurred more than 2 months after the initial mefloquine and halofantrine treatment (78 and 106 d, respectively) and would not have been detected in the usual 28 d observation period.

We conclude that double infections with *P. falciparum* and *P. malariae* may pose some therapeutic difficulties when treated with mefloquine or halofantrine. Since there has been little experience to date with these 2 drugs in quartan malaria, recrudescence of *P. malariae* after such mixed infections should be treated with chloroquine, which remains the treatment of choice. It is particularly important to make a thorough species diagnosis in such cases before treatment is given.

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