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Mefloquine: the benefits outweigh the risks

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Believe nothing that you see in the newspapers—they have done more to create dissatisfaction than all other agencies. If you see anything in them that you know is true, begin to doubt it at once (Sir William Osler).

Introduction

Falciparum malaria remains one of the world's biggest killers, accounting for about 2.1 million deaths in 1995—about 4% of all global mortality. The data are even more appalling than at first glance since most deaths are of children aged under 5 years. The vast majority of malaria deaths are in Africa, where the really big issue is preventing mortality rates from rising in the setting of global warming, worsening drug-resistance, severe poverty, rising population pressure and 'competing' disease targets, like acute respiratory infection, TB and diarrhoeal illnesses.

Inhabitants of developed nations live, for the most part, in non-endemic areas of the world and become exposed only when they choose to travel—for pleasure, business or war. Most, if not all, antimalarial drugs have been developed with such travellers, mainly soldiers, in mind [1]. One such drug, mefloquine, has replaced global malaria mortality as a 'medical headline' recently because of the supposedly unacceptable frequency of symptomatic toxicity in travellers. As a result, medical practitioners and patients alike are confused about the advisability of prescribing or taking mefloquine for malaria prevention.

Background

In its search for prophylactic drugs for US servicemen, which was accelerated by the war in Vietnam, the Walter Reed Army Institute of Research screened over a quarter of a million compounds between 1963 and 1976, and mefloquine was one of the more successful products. Its subsequent development to the market was entrusted to Hoffman LaRoche which introduced mefloquine (Lariam) in the mid-1980s for both the treatment of uncomplicated malaria and for prophylaxis.

The drug's mode of action against *Plasmodium falciparum* is unknown, but its effects are confined to the pathogenic blood stages of the parasite. Mefloquine is extensively absorbed from the gut, reaching maximum concentrations after about 2 h. It is very lipid-soluble and has a large apparent volume of distribution but, even so, partition across the blood : brain barrier is not extensive and mefloquine is not detectable in the CSF. The drug is very slowly eliminated, mainly as a carboxylic acid metabolite, with a half-time of about 1 month. It is excreted in breast milk [2].

Mefloquine is effective against many isolates of chloroquine-resistant *P. falciparum*, and has become the drug of first-choice for uncomplicated malaria in many parts of SE Asia. Resistance to mefloquine is well-recognised and worsening in SE Asia, but is not yet universal. In Africa mefloquine is little used, mainly because of its high cost; the parasites, for the most part, retain sensitivity.

Risk : benefit assessment

All therapeutic drugs have adverse effects: these may be dose/concentration-related or idiosyncratic (much less common, with less relationship to dose and greater risk because of their unpredictability). The physician's job, of course, is to balance anticipated benefit against possible risks.

Few would dispute that, faced with established *P. falciparum* parasitaemia (especially in non-immune subjects), the risks of the disease massively outweigh risks of drug treatment. It is in the setting of chemoprophylaxis—where the patient is disease-free—that such risk : benefit 'analysis' becomes particularly relevant and, very often, quite difficult. *P. falciparum* can be transmitted in most tropical countries, but the intensity of transmission is highest in sub-Saharan Africa, particularly in west Africa. Most British malaria deaths are 'imported' from Kenya because of its frequency as a holiday destination. African parasites are usually chloroquine-resistant but are sensitive to other drugs at the moment. In contrast, the main tourist destinations of SE Asia pose a much lower threat of malaria transmission, but there are exceptions (for detailed advice see Bradley & Warhurst [3]): parasites from SE Asia are not only chloroquine-resistant but are often multi-drug-resistant.

Overall, mefloquine is the drug of choice for travellers at high risk of acquiring chloroquine-resistant *P. falciparum*, and gives greater protection than other drugs in sub-Saharan Africa. However, because of concerns about

teratogenicity during the first trimester [concerns which are not backed up by human data (see Phillips-Howard & Wood [4])] mefloquine is not recommended for use by pregnant women or those women planning pregnancy within 3 months of the drug. This latter recommendation reflects the drug's very slow elimination from the body.

The mefloquine data sheet

The newly re-written data sheet for mefloquine lists the following as contraindications:

- Renal insufficiency and severe impairment of liver function.
- A history of seizure or psychiatric illness.
- Known hypersensitivity.
- Co-administration with halofantrine
- Pregnancy—other than in the presence of compelling medical reasons.
- Breast-feeding mothers.

The data sheet goes on to advise caution under the following circumstances:

- Women planning pregnancy.
- Young children
- Patients with cardiac conduction disorders
- Those undertaking tasks requiring fine coordination (including airline pilots).

Adverse reactions to mefloquine

'Classical' idiosyncratic reactions to mefloquine—often dermatologic and sometimes life-threatening—are reported during prophylactic mefloquine use [5, 6] but do not appear to be particularly common. In this respect mefloquine differs from amodiaquine or Fansidar (pyrimethamine-sulphadoxine), where severe idiosyncratic reactions are unacceptably frequent during chemoprophylaxis and neither drug is recommended for prophylactic use any longer.

In the doses used for treating malaria (15 to 25 mg kg^{-1} as a split dose during one day) dose-related adverse effects are quite frequent with mefloquine and can interfere with therapy. Early vomiting, which is a major problem because of the need for repeat treatment, occurs in about 7% of patients and is particularly likely with: higher doses, patients aged <6 or >50 years, high fever, and high parasitaemia. Anorexia, nausea, dizziness and sleep disorders are also seen more commonly with higher mefloquine doses [7]. Convulsions, other transient acute neurological problems and psychosis can all complicate falciparum malaria and are therefore difficult to attribute to a drug in that setting with certainty. Even so, it does seem clear that mefloquine can cause these reactions in a dose-related manner.

The adult prophylactic dose of mefloquine is 250 mg (about 3 to 5 mg kg^{-1}) which is one third of the dose used for treatment, but on a weekly basis. Because of its slow rate of elimination the drug accumulates with each dose, but even so steady-state levels are lower than those achieved very rapidly after 'therapeutic' doses. Concentration-related adverse effects would therefore be expected to be less frequent than during therapeutic use. The current controversy concerns the frequency with which prophylactic mefloquine is associated with symptomatic adverse events—particularly neuropsychiatric ones (including fatigue, headache, dizziness, sleep disturbance, hallucinations, changes in affect and frank psychosis).

Some scientific journals and the popular media, have recently aired concerns about the safety of prophylactic mefloquine, and we are told in one article that: 'Lariam fends off malaria more effectively than any other drug, but growing evidence of disturbing side effects may soon land its manufacturer in court' [8]. Strong stuff. In this article, Thompson [8] cites the numbers of spontaneous adverse reaction reports, two case histories (one of them being a case of 'Lariam-induced chronic fatigue syndrome'), impending litigation by 450 previous mefloquine-users and some opinions from medical experts (see also Cook [9]). We are also told by Thompson [8] that 'when members of the (malaria) advisory committee were asked whether they would personally take Lariam, they were divided 50:50 down the middle'. Were this true, it would leave one wondering what proportion of the committee avoids British beef! It has to be said that the data do not support the semi-anecdotal view that symptomatic, non-life-threatening adverse effects are common enough with prophylactic mefloquine to prompt the drug's avoidance in this setting.

In the present issue of the journal (pp. 415–421) the reader will see data from a double-blind, randomised, placebo-controlled trial in which prophylactic doses of mefloquine induced no symptomatic adverse effects at all, except self-limiting diarrhoea [10]. Furthermore, the report from Davis and colleagues is largely in-keeping with previously published findings. I shall summarise three such large studies. (1) Lobel and colleagues [11] compared long-term mefloquine prophylaxis with other drug regimens, examining efficacy (in sub-Saharan Africa) and tolerability: weekly mefloquine was 94% more effective than chloroquine, 84% more effective than chloroquine plus proguanil and as well tolerated as either of the other two regimens. (2) Steffen & colleagues [12] gave in-flight questionnaires to all subjects returning to Europe from Kenya in 1985 and 1991, and 145,003 people completed the survey. Prophylactic effectiveness was 91% for mefloquine, 82% for Fansidar, 72% for chloroquine-proguanil and no better than 42% for chloroquine alone. Adverse effects, which were usually mild, were of similar prevalence in all groups: 18.8% with mefloquine, 18.6% with chloroquine, 30.1% with chloroquine-proguanil and 11.7% with Fansidar. (3) Boudreau & colleagues [13] conducted a double-blind comparison of the tolerability of prophylactic doses of mefloquine or chloroquine in 359 servicemen. There was no compromise in function due to dizziness or incoordination in those given mefloquine and, the authors conclude, 'overall both weekly mefloquine and loading-dose mefloquine were well tolerated'. It should be noted however that sleep disturbance,

increased dream activity and 'depressive feelings' were more frequent in the mefloquine-treated subjects than in those who took chloroquine in this study.

What credence, then, should be given to anecdotal statements that doctors have 'had a colossal number of people with memory loss, disorientation, panic attacks, psychosis and epileptic fits' [8]? The spontaneous reporting of adverse drug reactions, often as letters to learned journals, is a valued part of our surveillance mechanism and there is no doubt that it should continue. However, the logical outcome of such observations should be a careful search for the prevalence rate of such reactions, their severity and outcome (perhaps leading to light being shed upon the rational mechanism for the adverse effect)—and not sensational reporting in the news-papers or on the TV. I contend that, in the case of mefloquine, we have enough reassuring data (to which we now add the paper by Davis *et al.* [10]) to favour the continued use of this effective drug for the prevention of chloroquine-resistant falciparum malaria in travellers at high risk of exposure. We should also bear in mind, when considering anecdotal reports of supposed drug-reactions, that symptoms such as fatigue, sleep-disturbance, headache and dizziness: (a) are extremely common presenting complaints in medical out-patient departments, both in the European Union and the USA, and are usually unrelated to drug therapy and (b) may be explained by travel-related factors other than drugs (as Davis *et al.* remind us) including alcohol, fasting, stress and sleep-deprivation.

Conclusion

Falciparum malaria can kill with remarkable speed, sometimes within a day of the onset of symptoms. Most of the available data suggest that prophylactic mefloquine is (a) the most effective chemoprophylactic drug for much of the tropics, (b) as well-tolerated as less-effective alternatives, (c) rarely the cause of life-threatening adverse effects but (d) relatively contraindicated in certain patients—listed in the data sheet. The cumulative total of malaria notifications to week 21 of 1996 shows a rise compared with data from 1995 [14], and people have voiced concern about a connection with the mefloquine 'scare' [15]. In fact, such a direct connection seems unlikely, but if the present 'scare' was to become generalised to all antimalarial drugs, we might well expect to see an increase in the incidence rate of imported malaria. The malaria advisory committee's updated recommendations on chemoprophylaxis are more keenly awaited than usual this year.

As a final thought, we would do well to remember that our difficulties with *Plasmodium falciparum* in the 'developed world' must be kept in perspective. In my opinion the focus of medical attention should remain in the tropics, where the real problem (controlling malaria) is to be found.

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