Development of mefloquine as an antimalarial drug*

UNDP/WORLD BANK/WHO UPDATE

The spread of multiresistant strains of Plasmodium falciparum *in south-east Asia and South America and the appearance of chloroquine resistance in Africa indicates the urgent need for alternative drugs against these parasites. Mefloquine, a 4-quinoline methanol, is the only new drug that is currently at an advanced stage of development.*

Studies in animal models and in the clinic have shown that it is highly active as a blood schizontocide against strains that are resistant to many established antimalarials, e.g., chloroquine and pyrimethamine. It is not, however, effective as a causal prophylactic agent. Preclinical toxicological, teratological, and carcinogenicity studies do not indicate any major contraindications to its use.

Intensive clinical studies have been carried out in Africa, North and South America, south-east Asia, and Europe. These studies have indicated that the compound is generally well tolerated, safe, and effective in the treatment of malaria, particularly infections with chloroquine-resistant parasites.

In order to protect this new and promising drug against the development of resistance to it in endemic areas, it is important that its introduction should be accomplished in a rational and deliberate manner. Appropriate precautionary measures include the development of mefloquine combinations (a combination of mefloquine with pyrimethamine–sulfadoxine is presently under investigation), its use with primaquine as a gametocytocidal drug to prevent transmission, and its deployment primarily for treatment, being used for prophylaxis only in special risk groups.

The spread of chloroquine-resistant falciparum malaria in south-east Asia, South America, and now in Africa and India, has posed very serious problems. It has been reported that over 90% of isolates in some parts of south-east Asia are now resistant to chloroquine. In India, until recently, chloroquine-resistant falciparum malaria was believed to be restricted to the north-east, but it is now realized that the problem is more widespread. In Africa, chloroquine resistance was reported in six countries in 1982. The problem of chloroquine resistance has been further compounded by the increasing prevalence of parasites resistant to the antifolate and sulfa drug combinations, particularly in

south-east Asia, where quinine resistance is also now being reported. This indicates the urgent need for alternative drugs active against chloroquine-resistant and multiresistant parasites.

The only new alternative antimalarial drug that is in an advanced state of development is mefloquine. This drug has been shown to be highly active against chloroquine-resistant falciparum strains in experimental animals and in man, and is also known to have a long half-life in man. Although mefloquine is by no means ideal, sufficient data are now available to show that it has a place in the treatment of malaria, particularly that caused by chloroquine-resistant *Plasmodium falciparum*. Even if another new drug were discovered today, it would take many years to bring it to the present status of mefloquine. Thus, it is possible that, in view of the serious situation posed by chloroquine-resistant malaria, some countries or adventurous pharmaceutical companies might try to introduce mefloquine independently, without considering some important issues and problems associated with the drug. This is a matter of grave concern for the successful use of mefloquine in the future.

It is appreciated that potentially valuable new drugs must be protected against the emergence of resistance to them. One of the ways this can be accomplished is through the judicious use of rationally selected drug combinations which, even if they do not completely prevent the development of resistance, can at least considerably delay it. For example, in rodents, it has been shown that *P. berghei* can easily develop resistance to mefloquine, especially if the parasites are already resistant to chloroquine, but that the rate at which this resistance develops can be reduced if mefloquine is administered in association with certain other antimalarials. These facts focus sharply on the need to prevent indiscriminate and uncontrolled use of mefloquine.

Although the clinical assessment of mefloquine is at an advanced stage, gaps still exist in the information available on its clinical use under certain situations. For example, it is recognized that malaria is much more severe in pregnancy, and also that the use of oral contraceptives may increase the severity of parasitaemia. The use of the sulfa-pyrimethamine combination in chloroquine-resistant malaria in pregnancy is controversial because of the suggestion of teratogenicity associated with high doses of pyrimethamine in the rat model. Thus, pregnant women infected with resistant strains of *P. falciparum* may be most in need of alternative drugs.

Chemotherapy is only one aspect of malaria control, but in view of the expense of comprehensive antimalaria programmes and spreading vector resistance to insecticides, it is becoming increasingly important. Sub-Saharan Africa, for example, is being forced to depend more and more upon chemotherapy. The need to associate malaria control strategies with the existing primary health care systems also places greater importance on drug treatment regimens.

For these reasons, and in the face of increasing resistance of falciparum parasites to standard antimalarials, it is necessary that the introduction of this new and promising anti-malarial be accomplished as rapidly as possible, but in a rational and deliberate manner.

PRESENT STATUS OF THE DEVELOPMENT OF MEFLOQUINE

Preclinical development of mefloquine

Animal models

Mefloquine, a 4-quinoline methanol, is a highly active blood schizontocide and is greatly superior to chloroquine in the *P. berghei*/mouse model. Strains of *P. berghei* that are

resistant to many established antimalarials, e.g., chloroquine and pyrimethamine, do not show cross-resistance to mefloquine. However, a strain highly resistant to quinine has shown appreciable resistance.

Mefloquine is also highly effective in the *P. cynomolgi*/rhesus monkey model, being comparable to chloroquine in potency but having a better therapeutic index. When tested in the owl monkey, strains of *P. falciparum* with different levels of natural resistance to established antimalarials were all susceptible to well-tolerated doses of mefloquine. The drug was equally effective whether administered in a single dose or in three fractional doses over as many days. Doses effective against *P. falciparum* in the owl monkey were also effective against *P. vivax*. Mefloquine, however, is not effective as a causal prophylactic or radical curative agent against sporozoite-induced relapsing malaria.

Pharmacology and toxicology

The results of acute, subacute, and chronic toxicity studies of mefloquine in the rat, dog, monkey, and mouse showed that:

— the drug was not mutagenic
— there were no teratological changes at doses that were tolerated by adult female animals
— toxic effects on the development of the offspring of rats were produced during the postnatal period only in those nursed by dams given very high doses of the drug
— the drug was not carcinogenic in rats or mice.

There was no evidence of toxic effects in dogs given doses of mefloquine ranging from 5 to 150 mg/kg of body weight once a week for a year. There was, however, a reduction in rate of increase in body weight in the animals given 25 mg or more of the drug per kg of body weight. In a similar study in rats, epididymal lesions were seen in the animals given 20 or 50 mg/kg of body weight per day for 90 consecutive days. The lesions were reversible in rats treated with 20 mg/kg of body weight, and reproductive performance in these animals was not impaired. Dogs and monkeys treated with mefloquine at doses of 5, 13.5, 30, or 68 mg/kg of body weight per day for 90 days had no lesions in the testes, prostate gland, or epididymis. Sperm counts and testosterone serum levels in dogs were not affected. Mefloquine given to mice for 24 months produced a greater incidence of gastritis and gastric mucosal hyperplasia, but only in females.

Mefloquine given to rats over 24 months caused a decrease in life expectancy at the highest dose used (30 mg/kg of body weight per day), and at this dose level caused lesions of the male sex organs and the retina. Mefloquine given at 5 mg/kg of body weight per day for a similar period was relatively non-toxic. The drug was not found to be phototoxic.

Pharmacokinetics and metabolism

Mefloquine is excreted predominantly in the faeces and bile. Five metabolites have been isolated and the structure of two identified as 2,8 bis-trifluoromethyl-quinoline-4-methanol and a carboxylic acid metabolite. These two metabolites, while inactive against *P. berghei* in mice, were tolerated in a manner similar to mefloquine when given orally to rats and mice.

Since the carboxylic acid metabolite was found in fairly large concentrations in the plasma, the levels of this and the parent drug have been determined in various species at steady state. The results indicated that the ratio of metabolite to mefloquine was high in mice, low in rats, and intermediate in man, i.e., in the range 2.3–8.6. Administration of the metabolite to the dog resulted in plasma levels ten times higher than those reached after administration of an equimolar amount of mefloquine. Steady-state plasma levels of the

metabolite were measured in human volunteers given a weekly dose of 250 mg of mefloquine. At the end of the trial, the half-life of the drug was found to be within the range previously measured in single-dose kinetics. The accumulation factor was between 3.6 and 6.7 in the five subjects studied.

Earlier studies raised the possibility of differences among ethnic groups in their metabolism of mefloquine. However, further work has not substantiated these observations. Half-lives are similar in Africans living in Europe or in Africa, in Caucasians, and in Brazilians.

Clinical trials

Clinical studies with mefloquine began in October 1972 with a phase I oral safety and tolerance study in Caucasians in the USA. Subsequently, similar trials have been carried out in Africa, Brazil, Europe, and India. Phase II and III trials have also been completed and it is hoped that the drug will be registered in the near future.

Tolerance studies in normal healthy male volunteers and in asymptomatic male patients have shown the appearance of dizziness, nausea, and vomiting, which occurred with increasing frequency as the dose exceeded 1000 mg of mefloquine (base) in the form of the hydrochloride. Better tolerance of doses between 500 and 1000 mg (base) was observed, with most side-effects being mild or moderate and occurring in the first few days following treatment. They were self-limiting, lasted for 24–48 h, and did not require specific treatment.

Out of a total of over 1000 patients, five cases of neuropsychiatric disturbances have been observed. Four were observed during trials in Bangkok and one in Ndola, Zambia. One of the four Thai cases showed such symptoms after the inadvertent administration of 2000 mg of mefloquine,[a] while the others were observed after 500 mg (one case) and 1000 mg (two cases). Symptoms occurred during the second week after drug administration, and included disorientation, hallucinations, and decreased consciousness. All patients recovered during the following two weeks without special treatment. Spinal fluid and EEG studies, when carried out, were normal and there was no history of similar episodes or of drug addiction. The symptoms of the patient in Ndola, who was given 1000 mg of mefloquine (base), also appeared during the second week of the study, on day 9 following drug administration. The patient was restless and uncooperative but conscious. Behavioural disturbances were minimal and the patient's condition quickly returned to normal.

Sinus bradycardia was observed in 6.8% of the patients from the phase II dose-finding study in Thailand and 13% of those in phase I, II, and III trials in Zambia. Bradycardia has not been described in patients in South America. In all cases, the pulse rate decreased 3–4 days after administration of the drug and returned to normal within two weeks. There were no overt symptoms and treatment was not required. ECG records did not show evidence of myocardial damage.

Clinical pharmacokinetic studies in male volunteers from Africa, Brazil, Europe, and the USA have shown that mefloquine has a long but variable plasma half-life of 6–23 days, with a mean value of around 14 days. Effective drug levels may persist for 30 days or more. This accounts for the therapeutic and long-term prophylactic efficacy of a single dose, but also suggests that there are likely to be occasional treatment failures as a result of host factors. Only limited data are available on the population kinetics of most antimalarial drugs, but variations in the estimated half-lives of chloroquine, sulfadoxine, and pyrimethamine are apparently less than those observed for mefloquine.

[a] HARINASUTA, T. ET AL. A phase II clinical trial of mefloquine in patients with chloroquine-resistant falciparum malaria in Thailand. *Bulletin of the World Health Organization*, 61: 299–305 (1983).

Phase II trials in oligosymptomatic adult males have been completed in Brazil, Burma, France, Gabon, Thailand, Upper Volta, the USA, and Zambia. The success of these trials and the results of recent mutagenicity and teratogenicity studies have now provided the basis for phase III studies in (a) male hospital patients with uncomplicated falciparum malaria, (b) females of child-bearing age, (c) pregnant women, and (d) children. Trials in men, women, and children were initiated in 1981/82 and some of these have recently been completed.

Dose-finding studies have been conducted in oligosymptomatic males suffering from falciparum malaria in Brazil, France, and Thailand, in children with falciparum malaria in Burma, and in patients with vivax malaria in France, the Philippines, and Thailand. As in the tolerance studies mentioned previously, side-effects such as vomiting, nausea, dizziness, etc. were observed more frequently and were more severe in patients given doses in excess of 1000 mg of mefloquine (base). However, vomiting was rarely seen in patients given 1000 mg (base) and not at all in those given 500 mg (base). In the Thai and Zambian trials, asymptomatic sinus bradycardia appeared to be dose-related, but was also observed in patients given chloroquine during double-blind randomized trials in Zambia.

The cure rate with all doses of mefloquine has been between 90% and 100% in all trials conducted so far and, although there is a tendency for the higher rates to be observed at the higher doses, it has not been possible to observe a significant difference between the various single-dose regimens. (Such an evaluation would require considerably larger sample sizes, especially in view of the low frequency of recrudescence.) When cases of incomplete sensitivity to the drug have been observed, the response of the parasite was predominantly of the RI type and was usually associated with the lower dose regimens. RII-type responses have been observed, but it is probable that these were related to vomiting following drug administration. RIII-type responses have not been observed. The majority of observations were made in areas with chloroquine-resistant or multiresistant *P. falciparum*.

Dose-related differences in rate of clearance of parasitaemia and of fever have been observed in all trials. For example, in a dose-finding study conducted in Thailand, the mean rate of clearance of parasitaemia was 49.6 h with a single dose of 1000 mg (base), 54.3 h with 750 mg (base), and 56.0 h with 500 mg (base) while the rates for fever were 29.3 h, 34.8 h, and 37.1 h, respectively.

Mefloquine has been compared with chloroquine for the treatment of asymptomatic falciparum malaria in a phase III trial involving 99 male subjects in Zambia. As a single dose of 1000 mg (base), it was well tolerated, effective, and safe. The cure rate was 98%, compared with 100% for chloroquine. The rate of clearance of parasitaemia was faster with chloroquine than mefloquine, but that for clearance of fever was similar for both drugs. There were no significant differences in safety, tolerance, and effectiveness of the two drugs, although one case of an RI-type response was observed in the mefloquine group, which may have been related to vomiting following drug administration.

Although a paediatric formulation for mefloquine has yet to be developed, limited trials in children have now been completed in Burma and the Upper Volta, using the tablet formulation. In the former study, doses of 20 and 30 mg/kg of body weight were compared in 89 patients. No significant differences were observed in either efficacy or tolerance of the drug in the two dosage groups. The mean parasite clearance time was 2.7 days in both groups. Four children (one given 20 mg/kg of body weight and three given 30 mg/kg of body weight) showed temporary reappearance of parasites on day 14 following administration, and two other children given the lower dose were not cleared of asexual blood forms within 7 days. They were, however, parasite-negative on days 15–28. This may reflect reinfection rather than recrudescence. Side-effects, mainly nausea, vomiting, and giddiness, were observed in approximately 60% of the children but this was not dose-

related. Preliminary studies on the pharmacokinetics of mefloquine suggest that the plasma half-life of the drug may be shorter in children than in adults.

Cure rates of 100% have been observed using single doses of 250–1500 mg of mefloquine base for the treatment of vivax infections. However, the number of cases observed in the trial was small. The follow-up period in this trial was seven days, but other trials have produced no clinical or parasitological evidence that mefloquine has any effect on the tissue stages of this parasite.

Thus, it can be concluded from the extensive clinical trials conducted predominantly in male subjects that mefloquine may be safe and effective in the treatment of both falciparum and vivax malaria, including infection with chloroquine-resistant *P.falciparum*.

The effect of various dosages of mefloquine and sulfadoxine–pyrimethamine in the suppression of malaria infection has been evaluated in an area of north-east Thailand that is highly endemic for both chloroquine-resistant *P.falciparum* and *P.vivax*. Mefloquine hydrochloride was administered in doses of 180 mg weekly, 360 mg weekly, or 360 mg every two weeks, while sulfadoxine–pyrimethamine was provided as 1 g of sulfadoxine and 50 mg of pyrimethamine given every two weeks, or 500 mg of sulfadoxine and 25 mg of pyrimethamine given weekly. Over 850 subjects completed the 6-month study. Mefloquine was a more effective suppressant of both species of parasite and there was no significant difference in infection rate between the dosage groups. There was no clinical evidence of drug toxicity in any group and the biochemical and haematological parameters measured were unaffected except for a significant increase in haematocrit in one group given mefloquine. Lower-than-normal leukocyte counts were observed in all groups but the only significant difference was between the biweekly sulfadoxine–pyrimethamine and placebo groups.

Development of mefloquine combinations

The emergence of resistance of malaria parasites to almost every antimalarial drug has been recognized as a major problem. One way of combating this problem has been to use drug combinations that have been shown to delay the development of resistance in animal models to one or all of the constituents. This has led to the use of combinations rather than single drugs for therapy and suppression, particularly in south-east Asia and Latin America. However, apart from sulfa–pyrimethamine combinations, these have been used empirically and as *ad hoc* combinations. It is, therefore, logical to search for appropriate mefloquine combinations.

Ideally, drugs used in combinations should be synergistic and pharmacokinetically compatible, i.e., they should have similar plasma half-lives and show no interaction. Unfortunately, there is no known drug that is synergistic with mefloquine, and mefloquine has a very long half-life which is difficult to match. However, work on the development of mefloquine combinations has been carried out, principally using a combination of mefloquine and sulfadoxine–pyrimethamine, the best pharmacokinetically matched combination available at present.

The chemotherapeutic response of *P. berghei* to different drug associations, e.g., mefloquine plus sulfadoxine–pyrimethamine mixtures, mefloquine plus primaquine, and mefloquine plus floxacrine, has shown that the effects are purely additive. These free combinations, especially with mixtures of sulfadoxine and pyrimethamine, have considerably delayed the development of resistance to the individual components in rodent malaria models.

Lines of *P. berghei* have been made resistant to single or combined drugs, including the mefloquine/sulfadoxine/pyrimethamine combination. With the exception of a pyrimeth-

amine-resistant line, resistance was unstable in the absence of drug pressure, and a line moderately resistant to the mefloquine/sulfadoxine/pyrimethamine combination was still sensitive to chloroquine, quinine, a quinine analogue (Ro 21-3473), and primaquine.

The toxicity of mefloquine combinations has been little studied, except for those containing sulfadoxine–pyrimethamine. Acute toxicity studies with this triple combination have shown no indication that the toxic effects of the individual components are potentiated, toxicity being purely additive.

It is difficult, however, to evaluate the combination for subacute or chronic toxicity since the tolerance in animals differs greatly according to the strain used and the diet of the animal. Moreover, the half-lives of the three drugs differ considerably between animal species and man so that the cumulation processes are different. Thus, before subacute or chronic toxicity studies could be carried out, dosage regimens had to be determined for the various species to give blood levels comparable with those seen in man. These studies are now in progress and, so far, have shown excellent tolerance in mice, rats, and baboons, with no serious toxic effects.

Fetotoxicity studies with the triple combination are now in progress. It is already known that mefloquine itself does not present a fetotoxic risk in mice, rats, or rabbits, but early experimental work in rats gave pyrimethamine the reputation of being a potentially fetotoxic agent. Although such side-effects were shown in the rat, the teratogenic potential of pyrimethamine was subsequently found to depend on the animal species involved and to be related to folate deficiency. In any event, teratogenicity proved to be preventable by administration of folate or folinic acid to the mother. It has been suggested that man has a lower susceptibility to these effects of pyrimethamine. No malformations have been observed in children born to mothers receiving high doses of pyrimethamine plus a sulfonamide for the chemotherapy of toxoplasmosis in the first trimester of pregnancy, and there have been no reports of such effects during the last two decades, when the pyrimethamine-sulfadoxine combination has been widely used.

The pharmacokinetics and metabolism of the triple combination have been studied in rats, rabbits, baboons, and man. The absolute bioavailability of the combination, when given orally, is unknown because of the lack of an intravenous injectable form. However, it appears to be satisfactory since, when given to volunteers, the plasma concentrations of the three components were indistinguishable from those observed after the administration of mefloquine or pyrimethamine–sulfadoxine tablets. The available data also do not indicate any difference in the metabolism or elimination of the components, whether they are administered in combination or singly. The plasma half-lives of the three drugs have been determined in six volunteers given the triple combination. They were all within the range of those observed after administration of the individual components. However, in view of the marked variation in the half-life of mefloquine, cross-over studies are now being conducted to compare the half-lives of the three components after administration of the combination and, at appropriate intervals, of the individual components to the same volunteers. This will establish whether the length of the half-life is related to individual differences in mefloquine binding to protein and subsequent slow release.

The results of this study may have considerable practical importance, not only in explaining occasional failures of mefloquine treatment, but also failures of triple-drug therapy using mefloquine with long-acting sulfonamide and pyrimethamine against *P.falciparum* infections. Drug failure occurs in around 10% of infected non-immune subjects receiving normally therapeutic doses of these sulfonamides, and is probably related to excessive plasma-protein binding and slow release resulting in protracted but subtherapeutic blood levels. Another metabolic abnormality, i.e., rapid acetylation of sulfonamides and rapid excretion, is disputed as a cause of drug failure. Patient immunity may, however, potentiate subtherapeutic blood levels to the point of efficacy.

Human tolerance studies of a triple combination containing 10 parts mefloquine to 20 parts sulfadoxine and 1 part pyrimethamine (i.e., tablets containing 250 mg of mefloquine (base), 500 mg of sulfadoxine, and 25 mg of pyrimethamine) are now in progress. Preliminary studies in two groups, given doses equivalent to one or two of the above tablets, showed no major subjective or objective clinical findings attributable to medication. Of the 8 subjects receiving the higher dosage, 4 had loose bowel movements, flatulence, and tinnitus 1–24 hours after medication, but the symptoms were mild and lasted for less than 24 hours.

FUTURE DEVELOPMENT OF MEFLOQUINE
AND MEFLOQUINE COMBINATIONS

Although mefloquine is already at an advanced stage of development, further trials in special risk groups are still required. In particular, the tolerance and bioavailability of the drug should be assessed in special risk groups in whom tolerance, drug availability, metabolism, and elimination may be affected. These groups include nutritionally deficient patients and persons with impaired liver function, diarrhoea, or severe acute malaria. Tolerance is currently being assessed in this last group; the study is also expected to give information on the pharmacokinetics and metabolism of the drug in such patients. It is also important that trials in pregnant women suffering from multiresistant *P. falciparum* infection should be initiated as quickly as possible, since this is a group in which the use of mefloquine appears to be indicated for ethical reasons.

Preclinical and phase I clinical studies of both an *ad hoc* and a fixed combination of mefloquine/sulfadoxine/pyrimethamine have already been undertaken. However, the phase I studies have so far been conducted only in normal healthy Caucasian and African subjects. These studies should now be extended to other racial groups in order to explore the tolerance and efficacy of the combination in the target population, and to assess its eventual usefulness as a complementary tool for the containment of multiresistant falciparum malaria.

While the combination of mefloquine with sulfadoxine and pyrimethamine is the only one being studied at this time, it would be wise to explore other potential combinations, especially for curative use. Although combinations, optimally matched as regards the half-lives of the constituents, appear to be the preferable formulation for field use, there will also be a need for mefloquine itself to be available.

FUTURE DEPLOYMENT OF MEFLOQUINE

Mefloquine will probably prove to be effective for the treatment or prophylaxis of all species of human malaria. However, the major indication for its use at present is in the treatment of patients infected with strains of *P. falciparum* resistant to chloroquine, particularly if the parasites are also resistant to sulfadoxine–pyrimethamine or similar combinations. Mefloquine should not be deployed for therapy when chloroquine resistance is not a problem, or for prophylaxis except in certain high-risk groups under special circumstances.

All possible measures should be taken to ensure that mefloquine is supplied only to countries where there are clear indications for its use as outlined above. These should be pursued through the World Health Organization, national governments, and the manu-

facturing industry. In particular, it is recommended that, in the countries concerned, strict governmental regulations should be established for its importation and distribution.

Before introducing mefloquine in any new area, all possible steps should be taken to determine the baseline sensitivity of local strains of *P. falciparum* to this drug, using the Rieckmann *in vitro* test as developed by WHO. Regular monitoring should be carried out after its introduction as long as transmission continues, and whenever a change in the clinical response to mefloquine is suspected.

This is already being carried out in Thailand where chloroquine-resistant *P. falciparum* malaria poses a serious problem, particularly in the east of the country where many parasites are also resistant to sulfadoxine–pyrimethamine predominantly at RI level. These parasite strains were first reported from Indochinese refugee centres located along the Thai–Kampuchean border. However, because of the massive internal migration of labourers within Thailand and the periodic replacement of military troops stationed in the border area, multiresistant falciparum malaria has spread to the extent that failure rates of up to 75% are now documented following standard sulfadoxine–pyrimethamine therapy of locally acquired infection near the western (Burmese) border and in the east.

The need for an effective antimalarial drug or combination in Thailand is thus critical. In 1980, more than 400 000 cases of malaria were documented in the country, of which 70% were caused by *P. falciparum* (the actual incidence may be considerably higher than the reported figure). In the eastern border provinces of Chanthaburi and Trad, which have relative falciparum prevalences of 87% and 94%, respectively, there have recently been increases in incidence of 80% and 300%, respectively. The situation along the Kampuchean border would seem to warrant the deployment of mefloquine.

It would be a serious mistake to depend on mefloquine any more than on any other antimalarial drug to control malaria indefinitely in the absence of other control measures. Any antimalarial drug should be used only as part of an integrated attack on the disease.

Comparative data on the response of *P. falciparum* to quinine in certain areas where multiple drug-resistant strains are prevalent are disturbing as they suggest that some quinine resistance is already present. Mefloquine is in the same chemical class as quinine and probably has a similar mode of action. In addition, mefloquine resistance has been shown experimentally to arise more easily from chloroquine-resistant strains than from sensitive ones. As mefloquine is most needed in the areas where multiple drug resistance occurs, this suggests that mefloquine resistance could arise quickly in the field. Mefloquine must therefore be protected, perhaps by using a triple combination of mefloquine with sulfadoxine–pyrimethamine for malaria treatment in areas of continuing transmission.

However, initial results in a rodent model have indicated that once a high level of resistance to pyrimethamine and sulfadoxine has developed, little is to be gained by the addition of mefloquine to the mixture. If the same holds true for *P. falciparum*, there may be no point in using the triple combination for prophylaxis or treatment in foci in which resistance to the sulfa/antifol combination has already reached a high degree. In this situation, it would be more rational to combine mefloquine with a single dose of primaquine since the potent gametocytocidal properties of this 8-aminoquinoline would prevent transmission. Thus, there is an urgent need to obtain data concerning the possible use of mefloquine in combination with primaquine as a gametocytocide and for the radical cure of vivax infections.

A single dose of 45 mg of primaquine base (adult dose), given with mefloquine used for therapy, would sterilize any existing gametocytes. This should help to decrease the transmission of parasites in areas where vectors are present, and hence minimize the risk of the emergence of drug resistance. It is essential and urgent that studies be undertaken to determine whether such an association of these two drugs would indeed reduce the transmission of malaria.

There is also an urgent need to find other compounds or drug mixtures to combine with mefloquine in view of the fact that, in at least one of the most problematic areas, Thailand, resistance already exists to sulfadoxine–pyrimethamine.

Mefloquine formulated alone should, of course, be available for the treatment of drug-resistant *P. falciparum* in pregnant women and in patients who do not tolerate sulfonamides or sulfones, or who live in areas without malaria transmission.