Chemoprophylaxis against malaria in eastern Thailand

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I. Introduction

1.1 The Global Malaria Situation

Malaria, a scourge of mankind through the centuries, has left its mark on world history, affecting the outcome of wars, movement of populations, and the growth and development of nations (1). A recent review of malaria worldwide indicated that over one-fifth of the population is living in originally malarious areas. Despite the impressive results of malaria eradication programmes sponsored by the World Health Organization in 1956, technical and socioeconomic difficulties have led to a resurgence of the disease in many parts of the world. Consequently, malaria remains today as it has been for centuries, one of the major problems in the world (3,4,5,6,7,8). Since the existing tools are clearly inadequate (3) one must hope that all of the available control measures will contain malaria transmission and buy time until more definitive methods such as immunization become available.

1.2 The Malaria Situation in Eastern Thailand

In Thailand, malaria remains the greatest public health issue, endangering not only the health of the population but also its overall socio-economic development (5). The fact is that where it was in rapid retreat, it is currently in resurgence (10).

Due to its natural resources and agricultural fertility, the eastern part of Thailand is economically our most important region, but is also the most endemic especially after the appearance of multidrug-resistant falciparum malaria. Therefore, we need to reassess the strategy for malaria drug therapy, both in the treatment of individuals as well as its use in malaria control program.

II. The present constraint for Chemosuppression:

2.1 Chloroquine-resistant falciparum malaria in Thailand

The resistance of P. falciparum to chloroquine has been reported in Thailand since 1962 (12). At approximately the same time, an American serviceman on temporary duty in Thailand contracted falciparum malaria and received many courses of chloroquine without achieving a radical cure (Young et al. 1968) (13). Subsequent drug sensitivity studies demonstrated that this strain was also resistant to mepracrine, proguanil, pyrimethamine and amodiaquine.

Harinasuta et al. (1965) (14) administered a conventional course of chloroquine (25 mg per kg) to infected patients. Only 2 (5%) of 42 patients experienced a radical cure. In a subsequent report by Harinasuta et al. (1967) (15), conventional chloroquine therapy was given to 65 hospitalized patients with P. falciparum infections. Not a single radical cure was achieved. The subjects examined in these 2 reports resided in many areas of
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Thailand and investigations suggested that strains of *P. falciparum* resistant to chloroquine were distributed throughout the entire nation. The prevalence and geographic distribution of chloroquine-resistant falciparum malaria in rural areas of Thailand were reported in 1966\(^{(18)}\). Bourke et al. reported a reduced sensitivity of *P. falciparum* to chloroquine among residents of 8 southern provinces bordering Malaysia. These field studies were extended by Cadigan et al. (1968)\(^{(17)}\) to other provinces in the southern, central and northcentral areas of Thailand. Infected subjects were given 25 mg per kg of chloroquine base and follow-up blood smears one week after the commencement of therapy. The proportions of unsatisfactory parasite responses ranged from 6% in the central provinces to 85% in the northcentral provinces.

During the early 1970's, in vivo and in vitro responses to chloroquine were measured in 57 patients infected with *P. falciparum* (Colwell et al. 1972)\(^{(18)}\). Treatment failures were observed in 55 (96%). All 57 individuals had parasites which exhibited chloroquine resistance in vitro. All investigations of the in vitro sensitivity of *P. falciparum* conducted in the northeast, southeast and southern provinces have yielded similar high rates of chloroquine resistant strains\(^{(19)}\). Segal et al.\(^{(20)}\) demonstrated that chloroquine was not efficacious either for hospitalized falciparum-infected patients or when given as suppressive prophylaxis. They also demonstrated that the high prevalence of chloroquine-resistant infections in the villages was similar to that found in hospitals and clinics. On conclusion, chloroquine-resistant falciparum malaria must have been prevalent throughout the country since the early 1970s\(^{(21)}\).

2.2 Emergence of sulfadoxine-pyrimethamine resistance

The combination of pyrimethamine (half-life about 96 hours) and sulfadoxine (half-life about 200 hours) at a fixed ratio of 1:20, marketed as "Fansidar", has been highly successful in preventing falciparum malaria when administered weekly\(^{(22)}\), two weekly\(^{(23)}\), or four weekly\(^{(22,24)}\). It was more effective than pyrimethamine with diformyladapson\(^{(26)}\) in a chemosuppressive field trial in Thailand.

This combination was also reported to be highly effective in the treatment of drug-resistant falciparum malaria in Thailand (Chin et al. 1978; Segal et al. 1975; Doberstyn et al. 1976; Doberstyn et al. 1978) and therefore considered in areas with chloroquine-resistant malaria to be the most effective commercially-available, single dose antimalarial drug in Thailand, during the past decade.

The regular use of "Fansidar" for suppressive management produces only occasional side effects. Three studies (Lucas et al., Muto et al., and Pearlman et al) observed isolated cases of asympto-
matic leukopenia which occurred only after prolonged uses of six months to one year. The authors stressed that the leukopenia was not severe and quickly regressed on cessation of medication. No skin reaction was observed with "Fansidar" when used in suppressive management.

The emergence in 1979 of P. falciparum malaria resistant to Fansidar in eastern Thailand has created a serious problem in malaria chemotherapy.\(^{(28)}\)

The widespread resistance to Fansidar was initially recognised in the Khmer refugee-camps along the Thai-Kampuchean border.\(^{(27)}\) Too many cases were reported to be attributable to drug failure and true parasite resistance to be developing.\(^{(28)}\)

The efficacy of Fansidar in the treatment of P. falciparum dropped markedly over the four-year period (1975-1979). Harinasuta et al.\(^{(29)}\) (1980) reported an 80% failure rate in P. falciparum carriers treated with sulfa-oxine and pyrimethamine. Recently Thaithong et al., in a study of the susceptibility of P. falciparum isolated from various parts of Thailand, showed very high resistances to pyrimethamine and chloroquine.\(^{(30,31)}\)

This serious situation has created an urgent need to reassess the strategy for malaria drug therapy, both for the treatment of individuals and the use in malaria control programmes.

III. Selection of the appropriate drug & dosage for collective prophylaxis in Eastern Thailand

With the appearance of multidrug-resistant falciparum malaria, a serious problem in malaria control in eastern Thailand has been created as the prophylactic recommendations made by W.H.O.\(^{(32)}\) and the Ross Institute\(^{(33)}\) (acknowledged sources of expertise) were no longer effective as prophylactic agents. The Center for Disease Control in Atlanta has recently recommended the use of quinine or tetracycline for the prophylaxis of these resistant strains.\(^{(34)}\) However, the main problem of this recommendation is that they are not based on well-established scientific evidences. There are no data on the efficacy of either quinine or tetracycline for the prophylaxis against resistant strains of P. falciparum currently transmitted in Thailand.\(^{(34)}\) These preventive drug regimens are relics of past experiences of P. falciparum resistant to chloroquine in Thailand.\(^{(18,35,36)}\)

IV. "Mefloquine", a new promising drug

4.1 Introduction

In response to an urgent need for effective drugs against multidrug-resistant strains of falciparum malaria, the most promising compound to emerge from the U.S. Army programme of research on antimalarial drugs is the "quinoline-methanol, WR 142,490"; this is now known by the generic name of "mefloquine".
This compound, which is at present undergoing extended clinical trials, has emerged from a programme in which over 250,000 compounds had been tested for the activity against drug-sensitive and drug-resistant malaria parasites since 1964. Six other compounds of these aminoalcohol series are being considered (87).

The drug has minimal side effects and is effective against all known strains of human plasmodia, including those resistant to chloroquine and quinine (despite its structural similarity to quinine). It was also found to be an outstanding suppressive prophylactic drug when administered weekly or fortnightly, in drug-resistant falciparum and vivax infections (88).

Mefloquine, which chemically is DL-erythro-α- (2-piperidyl)-2,8-bis- (trifluoromethyl)-4-quinolinemethanol hydrochloride, is structurally related to quinine, and was developed from SN 10275, a highly active antimalarial that was also extremely phototoxic. Phototoxicity was eliminated by the substitution of the phenyl group on the quinoline ring by a trifluoromethyl group (89,40).

Mefloquine is effective against the erythrocytic stage of all species of malaria parasites in a similar manner to quinine (41). The mechanism of action is still unknown. But unlike quinine and a number of other antimalarials, it does not intercalate with DNA (41,42). It is clear from experiments in the rodent model (41,42) the Aotus monkey, and in man (43) that mefloquine has no causal prophylactic activity, nor does it appear to have any action on the secondary tissue schizonts of P. vivax (48,44).

4.2 In vitro models
In an in vitro drug screening system, mefloquine was very active against a multi drug-resistant strain of Plasmodium (40).

4.3 In animal models
Its synthesis, and activity in animal models were described by many authors (42,45,46,47). In rodents, mefloquine is a potent blood schizontocide active against drug sensitive and drug resistant lines of P. berghei. Mode of action is similar to quinine both in vitro and in vivo, but is some 100 times more potent. Mixtures of mefloquine with pyrimethamine, sulphasphenazole or primaquine have an additive effect.

In the owl monkey system, Schmidt (46) found that this drug was active against multidrug-resistant strains of P. falciparum and was also effective in clearing blood parasites in P. vivax infections, although it did not effect a radical cure in sporozoite-induced P. vivax.

4.4 Pharmacokinetic observations
Metabolic studies in laboratory rodents (48,49) have shown that the drug is well absorbed, widely distributed, with a high affinity for biliary and lymphoid tissues, and excreted predominantly in feces (49). The disposition of mefloquine
was compared to that of quinine. Mefloquine was more highly bound and exhibited a longer half-life than quinine.

Pharmacokinetic studies in man, have shown mefloquine to have a prolonged half-life. Normal volunteers (not infected with malaria) had a mean whole blood half-life of 18.89 days, with a range of 6.48–22.54 days\(^{50}\).

4.5 Preliminary clinical trials in infected volunteers

Mefloquine has been used successfully in volunteers infected with chloroquine-sensitive and multidrug-resistant strains of P. falciparum\(^{51}\). Four volunteers received 1 gram of mefloquine as a single dose and 14–16 days later were challenged by mosquitoes infected with P. falciparum. None of the four developed patent infection. Three other subjects, who received 1 gram of mefloquine and were challenged on day 21, did develop malaria but not until 17–85 days later\(^{51}\). Clyde et al.\(^{53}\) further tested the suppressant effect of mefloquine on sporozoite-induced malaria in non-immune volunteers. Single doses of 250 mgs were given at weekly intervals, 500 mgs at intervals of 2 weeks and 1,000 mgs at intervals of 4 weeks. The study-subjects were challenged with mosquitoes heavily infected with a chloroquine-and pyrimethamine-resistant strain of P. falciparum. None of the individuals developed infections during the follow-up period of 60 days. Doses of 250 mgs or 500 mgs produced no adverse reactions. Sporozoite-induced P. vivax infections were suppressed by single-doses of 250 mgs of mefloquine given at weekly intervals.

4.6 Hospital Studies

The hospital studies conducted in Thailand evaluated the effect of single 1.5 gram doses on naturally acquired P. falciparum infection. Cure rates of 94%\(^{62}\) and 100%\(^{68}\) were obtained. Gastrointestinal side effects (nausea, vomiting and diarrhea) in some patients following the large single oral dose were noted in the reports of these studies, but were generally mild and self-limited. Hall et al.\(^{64}\) has also studied the sequential treatment with a short course of quinine, followed by a single 1.5 gram dose of mefloquine for patients with chloroquine-resistant falciparum malaria, including those with severe or complicated disease. The cure rate was 100%.

4.7 Extended field trials

Prior evaluation of prevention strategies suggested that the drug would be especially useful as a chemosuppressive agent\(^{38,61,48}\). Mefloquine was found to be more effective than sulfadoxine-pyrimethamine in the suppression of both falciparum and vivax parasitaemias. Complete suppression in both falciparum and vivax parasitaemia was seen in subjects who received mefloquine (360 mgs) fortnightly. There was no apparent difference between the three mefloquine dosage schedules. Therefore, the recom
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Smrkovski et al.\(^{(58)}\) reported the possible presence of local strains from the Phillipines of P. falciparum resistant in vitro to mefloquine.

Recently, there are also reports of mefloquine resistance in the treatment of P. falciparum in Thailand\(^{(59)}\), and Tanzania\(^{(60)}\) where the drug has not even been used.

Therefore, every possible precaution should be taken to protect this potentially invaluable new compound.

VI. Prevention of drug resistance

Two ways of slowing down the rate at which malaria parasites become resistant to new antimalarial drugs are to limit their use or to use a drug combination\(^{(60,61)}\) — a principle long accepted in the management of conditions such as tuberculosis, but still reluctantly considered in other fields\(^{(61)}\).

Strict government drug control is the logical, but unfortunately unrealizable step that should be taken. Drug control is, in practice, little enforced or unenforceable in those very countries where problems of drug resistance are most acute. A black market in drugs is common even where attempts are made to control their distribution and use by the population. Fansidar, for example, is freely available on the black market in the Kampuchean refugee camp in Thailand\(^{(57)}\), and even mefloquine, which in theory, is available at present only for authorized clinical trials, is also said to be circulating in this manner\(^{(61)}\).

4.8 Toxicity and Side Effects

Mefloquine, given orally in single doses of up to 1500 mgs, or as a 500 mg dose weekly for one year, is well tolerated in man. There were no significant changes in the blood count or chemistry. Due to lack of information, the use of Mefloquine in women, infants, and children is not recommended\(^{(58)}\).

V. Future problems for antimalarial drugs

Judging from laboratory studies on Plasmodium exhibiting resistance to mefloquine, this drug is unlikely to remain effective for long in south-east Asia, especially if used alone\(^{(58)}\).

Brockelman et al.\(^{(58)}\) have shown that the "misuse" of mefloquine in culture, i.e., at a concentration lower than prescribed and with early termination of treatment, caused a Plasmodial decrease in sensitivity to mefloquine within three months. Therefore, when mefloquine is commercially available, it too might soon become ineffective.

In rodent malaria, mefloquine resistance may begin to emerge in a chloroquine resistant strain after only one passage, under drug pressure\(^{(57)}\).
This experience lends strong support to the view that mefloquine should be used only in combination with another effective antimalarial drug. Clearly, it would be more satisfactory if we discover a drug that could both potentiate mefloquine (as well as) slowdown the rate to which parasites become resistant.

VII. The logistically feasible combinations

7.1 Combination of Mefloquine and Quinine (or Tetracycline)

Although, as already stated, the Center for Disease Control in Atlanta has recommended the use of quinine or tetracycline in the prophylaxis of multidrug-resistant falciparum malaria, using either in combination with mefloquine is not logistically feasible at this time because

a) there is no data on the efficacy or tolerance of this combination;

b) the half-lives of the individual components are not well matched (mefloquine 333 hours, quinine 10 hours, tetracycline 9 hours). Mefloquine can be administered every 1 to 2 weeks for prophylaxis, but quinine or tetracycline has to be given 3 to 4 times a day.

7.2 Combination of Mefloquine with Pyrimethamine/Sulfadoxine

Pyrimethamine and Sulfadoxine each inhibit different enzymes in the plasmodial folate biosynthetic pathway. However, either combination is theoretically unsuitable to prevent the development of resistance, since the resistances to these drugs are easily induced and already widespread by the time the combination will be introduced. The ideal would be a combination of two drugs, each effective when used alone with no evidence of cross resistance, and each given in full dose.

Seen in this light, Fansidar should be considered as a single drug and should be combined with another effective antimalarial to which resistance has not yet appeared. Given its long half-life and high effectiveness to date, mefloquine could fill such a role. The synergistic antiplasmodial effect of pyrimethamine and sulfadoxine can be enhanced by the additive effect of mefloquine. The use of the triple combination results in a marked delay of resistance development and, because of the lower dosages, in better tolerance and fewer side-effects. Furthermore, the half-life of the individual components are well matched since the half-life of sulfadoxine is 200 hours, of pyrimethamine 96 hours, and mefloquine about 333 hours; this combination can be administered prophyllactically every 2 weeks, which is long enough to maintain the acceptance and high compliance of drugs by the population.

In vitro, the inhibitory activity of mefloquine in combination with pyrimethamine/sulfadoxine against P. falciparum in continuous cultures has been studied in Thailand. P. Falciparum collected from the peripheral blood of infected persons and maintained in continuous culture usually shows a decrease in sensitivity to mefloquine. Cultivation of the drug-sensitive line in a medium containing increasing concentrations of
mefloquine produced a new line which was resistant to mefloquine. However, such an attempt failed when it was carried out in the presence of pyrimethamine-sulfadoxine. Therefore, it would be sensible to administer mefloquine in combination with Fansidar in order to avoid the wide-spread selection of P. falciparum with reduced sensitivity to mefloquine.

Studies at the London School of Hygiene and Tropical Medicine have also shown that the response of P. berghei to mefloquine in association with other antimalarials is at least additive (probably even potentiating) and that triple combinations, especially of pyrimethamine and sulfadoxine, have pronounced delaying effects on the development of resistance to the individual components.

Pharmacokinetic studies in 2 groups of 8 healthy adult men, have found no interference within the combination, using 750 mgs mefloquine 75 mgs pyrimethamine and 1.5 gm sulfadoxine, compared with placebo.

Preclinical studies on such a combination, in the ratios determined by CHEMAL in consultation with the industry, have been carried out and allowed CHEMAL to complete phase I tolerance and pharmacokinetic (bioavailability) studies in Belem and in Ndola.

Various phase II and III studies, mostly coordinated by WHO are being carried out in South East Asia, South America and Zambia, using a fixed combination of 250 mg mefloquine (base), 500 mg sulfadoxine and 25 mg pyrimethamine per tablet. The preliminary results with regard to tolerance and efficacy are very promising. Recently, clinical trials have been conducted in Thailand using mefloquine 750 mg plus 75 mg pyrimethamine and 1.5 gm sulfadoxine (3 tablets of Fansidar) compared with mefloquine 750 mg alone for treatment of falciparum malaria. The preliminary results with regard to tolerance and efficacy are also very promising in both groups. Therefore, this combination appears logistically feasible at this time.

VIII. Conclusion

Eastern Thailand, an important agricultural region, is known to be a highly malarious area. The appearance of multidrug-resistant falciparum malaria has created a serious problem in malaria chemotherapy and chemoprophylaxis. Although mefloquine, a representative of a new class of antimalarial agent is promising for the chemoprophylaxis of these multidrug-resistant strain of P. falciparum, judging from laboratory studies, this drug is unlikely to remain effective for long especially if used alone. One of the most practical ways to slow down the development of resistance is to use mefloquine in combination with other drugs. Combination with sulfadoxine-pyrimethamine appears appropriate at this time.

However, in using this combination as a chemoprophylaxis one should assess
the possible harm done in the form of increased mefloquine/Fansidar resistance by continuously monitoring this possible risk at the earliest time; the most important strategy at present is to save this potentially invaluable new compound for treatment purposes.

Hopefully too, a malaria vaccine may eventually open new possibilities in the immunoprophylaxis of malaria (19). In the meantime, we have to rely on the best available control measure to buy time until other more definitive control methods become available (2).

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