บทฟื้นฟูวิชาการ

# Chemoprophylaxis against malaria in eastern Thailand

Pirom Kamol-Ratanakul[*]

ภิรมย์ กมลรัตนกุล. ยาป้องกันไข้มาลาเรียสำหรับภาคตะวันออกของประเทศไทย
จุฬาลงกรณ์เวชสาร 2527 พฤศจิกายน ; 28(11) : 1311–1324

    ภาคตะวันออกของประเทศไทย เป็นภาคที่มีความสำคัญทางด้านเศรษฐกิจ แต่
เป็นที่น่าเสียดายว่าพื้นที่ส่วนใหญ่ของภาคนี้จัดเป็นแดนมาลาเรีย และเป็นมาลาเรีย
ชนิดที่ดื้อต่อยาที่ใช้รักษาไข้มาลาเรียแทบทุกชนิดที่ใช้กันอยู่ในปัจจุบัน ทำให้เกิดปัญหา
ในการเลือกใช้ยาสำหรับการควบคุมและป้องกันโรคนี้

    จากการศึกษารายงานต่างๆ พอสรุปได้ว่า ยาเมโฟลควิน เป็นยาที่มีประสิทธิภาพ
ดีและน่าจะเหมาะสมสำหรับใช้ในการรักษา ควบคุมและป้องกันไข้มาลาเรียในขณะนี้
แต่การใช้เมโฟลควินเพียงอย่างเดียวอาจก่อให้เกิดปัญหาเชื้อดื้อยาขึ้นในอนาคต ดังนั้น
การใช้ยาเมโฟลควินร่วมกับยาซัลฟาด๊อกซีนและไพริเมธามีนน่าจะเหมาะสมที่สุด ทั้งใน
แง่ประสิทธิภาพ การป้องกันการดื้อยา และความสะดวกในการใช้ป้องกันเพราะสามารถ
ให้ทุก 2 สัปดาห์ แต่ถึงกระนั้นก็ตามการใช้ยาทั้ง 3 นี้ร่วมกันในการป้องกันไข้มาลาเรีย
อาจก่อให้เกิดปัญหาขึ้นในอนาคตโดยเฉพาะ ปัญหาเรื่องเชื้อดื้อยา ดังนั้นจึงจำเป็นต้อง
มีการประเมินผลในแง่มุมต่าง ๆ ก่อนการตัดสินใจกำหนดเป็นนโยบายระดับชาติ

*  Department of Preventive & Social Medicine, Faculty of Medicine, Chulalongkorn
   University.

# 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[2] 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[9]. 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 Chemo-suppression :

## 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 mepacrine, 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

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[16]. 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 diformyldapsone[25] 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[26].

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 sulfadoxine 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[37].

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[38].

Mefloquine, which chemically is DL–erythro–$\alpha$– (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[39,40].

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[40] 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 appear to have any action on the secondary tissue schizonts of P. vivax[43,44]

### 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, sulphaphenazole 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 choroquine-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 develope malaria but not until 17-85 days later[51]. Clyde et al[43] 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%[52] and 100%[53] 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[54]. 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[38,51,43].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

mended dose for suppressive prophylaxis in Thai adults (average weight 50 kgs) was 180 mgs weekly, or 360 mgs every 2 weeks. Based on these dosage, the equivalent regimen for a 70-kg American adult would be 250 mg weekly, or 500 mgs 2 weekly. No serious side-effects have been associated with the use of mefloquine[38].

### 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[55].

### 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[28].

Brockelman et al[56] 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].

Smrkovski et al[58] reported the possible presence of local strains from the Phillippines 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[27], 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].

This experience lends strong support to the view that mefloquine should be used only in combination with another effective antimalarial drug[62]. 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[65]. 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 halflife of the individual components are well matched since the halflife of sulfadoxine is 200 hours, of pyrimethamine 96 hours, and mefloquine about 333 hours; this combination can be administered prophylactically 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[68]. 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[64] 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[65]. Recently, clinical trials have been conducted in Thailand[66] 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[67]. 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].

## References

1. Beck JW, Barret-Cornor, E. Malaria in Medical Parasitology. Saint Louis : C.V. Mosby, 1981

2. Wernsdorfer WH. The importance of malaria in the world. In : Kreier JP, ed. Malaria I. Toronto : Academic Press, 1980

3. World Health Organization. Eradication in 1972. WHO Chron 1973; 27(12) : 516

4. World Health Organization. The malaria situation in 1973. WHO Chron 1974; 28(11) : 479

5. World Health Organization. The malaria situation in 1974. WHO Chron 1975; 29(12) : 474

6. World Health Organization. The malaria situation in 1975. WHO Chron 1976; 30(12) : 486

7. World Health Organization. The malaria situation in 1976. WHO Chron 1978; 32(1) : 9-17

8. World Health Organization. Malaria control-A reoriented strategy. WHO Chron 1978; 32 : 226-230

9. Ministry of Public Health. Thailand Health Profile, 1980.

10. Malaria Division, Department of Communicable Diseases Control, Ministry of Public Health, Bangkok, Thailand. General information on the antimalaria programme in Thailand, 1982

11. Bruce-Chwatt LJ, Black RH, Canfield CJ. Chemotherapy of Malaria. 2 ed. WHO Monograph Ser. No. 27, 1987

12. Harinasuta T, Migasena S, Bunnag D. Chloroquine resistance in plasmodium falciparum in Thailand, UNESCO 1st Regionalsymposium on Scientific Knowledge of Tropical Parasites, Singapore, 1962. 148

13. Young MD, Contacos PG, Stitcher JE, Millar JW. Drug resistance in plasmodium falciparum from Thailand. Am J Trop Med & Hyg 1963 May; 12(3) : 305-314

14. Harinasuta T, Suntharasamai P, Viravan C. Chloroguine-resistant falciparum malaria in Thailand. Lancet 1965 Oct 2 ; 26(7414) : 657-660

15. Harinasuta T, Viravan C, Reid HA. Sulphormethoxine in chloroquine-resistant falciparum malaria in Thailand. Lancet 1967 May 27 ; I (7500) : 1117

16. Bourke ATC, Puhomeharoen S, Cadigan FC, Gould DJ. Prevalence of malaria exhibiting reduced sensitivity to chloroquine in Southern Thailand. Trans R Soc Trop Med & Hyg 1966; 60(2) : 225-230

17. Cadigan FC, Sadudee N, Bourke ATC, Gould DJ. Surveys on chloroquine-resistant P. falciparum in Thailand. Trans R Soc Trop Med & Hyg 1968; 62(4) : 562-566

18. Colwell EJ, Hickman RL, Kosakul S. Tetracycline treatment of chloroquine-resistant falciparum malaria in Thailand. JAMA 1972 May 1 ; 220 (5) : 684-686

19. Colwell EJ, Phintuyothin P, Sadudee N, Benjapong W, Neoypatimanondh S. Evaluation of an in vitro technique for detection chloroquine resistant falciparum malaria in Thailand. Am J Trop Med & Hyg 1972 Jan; 21(1): 6-12

20. Segal HE, Gresso WE, Thiemanun W. Longitudinal malaria studies in rural Northeast Thailand : chloroquine treatment of falciparum malaria infections. Trop Geogr Med 1975 Jan; 27(2) : 160-164

21. Harinasuta T, Gilles HM, Sandosham AA. Seameo-Tropmed Scientific Group Meeting. East Asia. Southeast Asian J Trop Med Public Health 1976 Dec; 7(4) : 641-684

22. Lucas AO, Hendrickse RG, Okubadejo OA, Richards WH, Neal RA. The suppression of malarial parasitaemia by pyrimethamine in combination with dapsone or sulphormethoxine. Trans R Soc Trop Med Hyg 1969; 63(2) : 216-229

23. Laing ABG. Malaria supression with fortnightly doses of pyrimethamine with sulfadoxine in the Gambia. Bull WHO 1970; 43 : 513-520

24. O'Holohan DR, Mathews JH, Malaria suppression and prophylaxis on a Malaysian rubber estate : sulformethoxine-pyrimethamine single monthly dose vs chloroquine single weekly dose. Southeast Asian J Trop Med Public Health 1971 Jun; 2(2) : 164-168

25. Pearlman EJ, Lampe RM, Thiemanun W, Kennedy RS. Chemosuppressive field trails in Thailand III. The suppression of plasmodium falciparum vivax parasitemias by a sulfadoxine-pyrimethamine combination. Am J Trop Med Hyg 1977 Nov; 26(6) : 1108-1115

26. Armed Forced Research Institute of Malaria Services, United States Army Medical Component, Bangkok, Thailand. Annual Progress Report, October 1979-September 1980

27. Hurwitz ES, Johnson D, Campbell CC. Resistance of plasmodium falciparum malaria to sulfodoxine-pyrimethamine (Fansidar) in a refugee camp in Thailand. Lancet 1981 May 16; 1 (8229) : 1068-1070

28. WHO Report of the Seventh Asian Malaria Conference. Malaria control and national health goals. WHO Tech Rep Ser 1982; 680 : 1-61

29. Harinasuta T, Bunnag D, Pinijpongse S. Abstracts of the Tenth International Congress of Tropical Medicine and Malaria, Quezon City, Philippines : PB Printing Press, 1980. 282

30. Thaithong S, Beale GH, Resistance of Thai isolates of plasmodium falciparum to chloroquine and pyrimethamine by in vitro tests. Trans R Soc Trop Med Hyg 1981; 75(2) : 271-273

31. Thaithong S, Beale GH, Chutmongkonkul M. Susceptibility of plasmodium falciparum to an in vitro study of isolates mainly from Thailand. Trans R Soc Trop Med Hyg 1983; 77(2) : 228-231

32. World Health Organization. Synopsis of the world malaria situation, 1979. Weekly Epidemiological Record 1981; 56(19) : 145-149

33. The Ross Institute. Malaria prevention in travellers from the United Kingdom : a report. Br Med J 1981 Jul 18; 283(6285) : 214-218

34. CDC. Prophylaxis against both chloroquine and pyrimethamine-sulfadoxine resistant strains of P. falciparum. MMWR 1982; 31(15) : 255-265

35. Clyde DF, Muller RM, Dupont HL, Hornick RB. Antimalarial effects of tetracyclines in man. J Trop Med Hyg 1971 Nov; 74(11) : 238-242

36. Rieckmonn KH, Powell RD, Mc Namara JV, Willerson Jr, Kass L. Effects of tetracycline against chloroquine-resistant and chloroquine-sensitive plasmodium falciparum. Am J Trop Med Hyg 1971 Nov; 20(6) : 811-815

37. Canfield CJ, Heiffer MH. The US Army drug development programme. In : Adolphe M, ed. Advances in Pharmacology and Therapeutecs. Oxford : Pergamon Press, 1978

38. Pearlman EJ, Doberstyn EB, Sudsok S, Theimanun W, Kemedy RS. Chemosuppressive field trials in Thailand IV. The suppression of plasmodium falciparum and plasmodium vivax parasitemias by mefloquine (WR 142, 490, a 4-quinolinemethanol) Am J Trop Med Hyg 1980 Nov; 29(6) : 1131-1137

39. Howells RE. Advances in Chemotherapy. Br Med Bull 1982; 38(2) : 193-199

40. WHO Scientific Group. Chemotherapy of malaria and resistance to antimalarials. WHO Tech Rep Ser 1973; 529 : 1-93

41. Davidson MW, Griggs BG, Boykin DW. Mefloquine, a clinically useful quinolinemethanol antimalarial. Which does not significantly bind to DNA. Nature 1975 Apr 17; 254(5501) : 632-634

42. Peters W, Howells RE, Portus J, Robinson BL, Thomas S. The chemotherapy of rodemt malaria, XXIII : studies on mefloquine (WR 142, 490). Ann Trop Med Parasitol 1977 Dec; 71(4) : 407-418

43. Clyde F, McCarthy VC, Miller RM. Suppressive activity of mefloquine in sporozoite-induced human malaria. Antimicrob Agents Chemother 1976; 9(3) : 384-386

44. Trenholme GM, Williams RL, Desjardins RE, Carson PE, Frischer H. Mefloquine (WR 142, 490) on the treatment of human malaria. Science 1975 Nov 21; 190(4216) : 792-794

45. Peters W, Devies EE, Robinson BL. The chemotherapy of rodent malaria, XXIII. Causal prophylaxis, part II : Practical experience with plasmodium yoelii nigeriensis in drug screening. Ann Trop Med Parasitol 1975 Sep; 69(3) : 311-328

46. Schmidt LH. Infections with plasmodium falciparum and plasmodium vivax in the owl monkey : model systems for basic biological and chemotherapeutics studies. Trans Rov Soc Trop Med Hyg 1973; 67(4) : 446-474

47. Warhurst DC. Chemotherapeutic agents and malaria research. In : Taylor AE, Muller R eds. Chemotherapeutic Agents in the Study of Parasites, Symposia of the British Society of Parasitology VII. Oxford : Blackwell, 1973 pp. 1-28

48. Mu JY, Israili ZH, Dayton PG. Studies of the disposition and metabolism of mefloquine HCl (WR 142, 490), a quinolinementhanol antimalarial, in the rat. Limited studies with an analog, WR 30,090. Drug Metab Dispos 1975 May-Jun; 3(3) : 198-210

49. Rozman RS, Molek NA, Koby R. The absorption, distribution, and excretion in mice of the antimalarial mefloquine, erythro-2, 8-bis (trifluromethyl)-a-(2-piperidyl)-4-quinoline-methanol hydrochloride. Drug Metab Dispos. 1978 Nov-Dec; 6(6) : 654-658

50. Desjardins RE, Haynes JD, Cheloy JD. Quantitative assessment of antimalarial activity by an automated in vitro system. Fed Proc 1978; 37 : 379

51. Rieckman KH, Trenholme GM, Williams RL. Prophylactic activity of mefloquine hydrochloride (WR 142, 490) in drug-resistant malaria. Bull WHO 1974; 51 : 375-377

52. Hall AP. The treatment of malaria. Br Med J 1976 Feb 7; 1(6005):323-377

53. Doberstyn EB, Phintuyothin P, Noeypatimanondh S. Single-dose therapy of falciparum malaria with mefloquine or pyrimethamine-sulfodoxine. Bull WHO 1979; 57 : 275-279

54. Hall AP, Doberstyn EB, Karnchanachetanee C. Sequential treatment with quinine and mefloquine or quinine and pyrimethamine–sulfadoxine for falciparum malaria. Br Med J 1977 Jun 25; 1(6077) : 1626–1628

55. Rolls IM. Drugs used in the chemotherapy of malaria, In : Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 6 ed. New York : Macmillan, 1980

56. Brockelman CR, Monkolkeha S, Tanariya P. Decrease in susceptibility of plasmodium falciparum to mefloquinein continuous culture. Bull WHO 1981; 59(2) : 249–252

57. Peters W, Portus J, Robinson BL. The chemotherapy of rodent malaria XXIII. The development of resistance to mefloquine (WR 142, 490). Ann Trop Med Parasitol 1977 Aug; 71(4) : 419–427

58. Smrkovski LL, Buck RL, Aleantara AK, Rodriguez CS. In vitro mefloquine resistant plasmodium falciparum from the Philippines. Lancet 1982 Aug 2; 2(8293) : 322

59. Boudreau EF, Webster KH, Pavanand K, Thosingha L. Type II mefloquine resistance in Thailand. Lancet 1982 Dec 11; 2(8311) : 1335

60. Bygbjerg IC, Schapera A, Flachs H. Mefloquine resistance of falciparum malaria from Tanzania enhanced by treatment. Lancet 1983 Apr 2; 1(8327) : 774

61. Peters W. Antimalarial drug resistance : an increasing problem. Br Med Bull 1982; 38(2) : 187–192

62. Editorial. Drug–resistant malaria. Lancet 1981 Nov 14; 2(8255) : 1087–1088

63. Tan–ariya P, Brockelman CR. The inhibitory activity of mefloquine in combination with sulfadoxine–pyrimethamine against Plasmodium falciparum in continuous culture, Abstracts of paper presented at the conference on malaria research, Pattaya, 25–27, April, 1983

64. Merkli B, Richle R, Peters W. The inhibitory effect of a drug combination on the development mefloquine resistance in plasmodium berghei. Ann Trop Med Parasitol 1980 Feb; 74(1) : 1–9

65. Wersdorfer WH. Recent progress in research on the chemotherapy of malaria, Abstracts papers presented at the conference on malaria research, Pattaya 25–27 April, 1983

66. Pinichpongse S, Doberstyn EB, Pantharvee C. Field trials of mefloquine in association with sulfadoxine/pyrimethamine and with a gametocytocidal dose of primaquine, Abstracts of papers presented at the conference on malaria research, Pattaya 25–27 April, 1983

67. Bruce–Chwatt LJ. Chemoprophylaxis of malaria in Africa : the spent "magic bullet" Br Med J 1982 Sep 11; 285(6343) : 674–676