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Treatment of drug resistant Falciparum Malaria in Thai Children and Adolescents

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Introduction

Resistance of *Plasmodium falciparum* to chloroquine in Thailand was first noted in the late 1950s (1). These infections were contracted in the Thailand/Cambodia border area and were, incidentally, the first to be observed in the Old World. Subsequently, chloroquine resistance increased, both in degree and frequency, and became a major problem in the early 1970s, necessitating a change of first line treatment. In view of the substantial incidence of falciparum malaria in Thailand, and the well known capability of *P. falciparum* to produce resistance to antimalarial drugs, a programme for the clinical-parasitological evaluation of antimalarial medications was established in the 1970s with the aim of optimizing and continuously updating the appropriate therapeutic recommendations. The results reported in this paper reflect observations in children and adolescents who are a special group inasmuch as pharmacokinetic and toxicological features are often different from those seen in adults.

Material and Methods

Between 1971 and 1987 more than 600 children and adolescents of 1 to 12 years of age were included in the drug regimen studies conducted by the Department of Tropical Paediatrics at the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. These mostly non immune patients originated from malarious areas, mainly from eastern and western border areas of Thailand (Bangkok and most of central Thailand are free from malaria transmission). Most investigations followed an open design with randomized group attribution, but where it was feasible they were conducted as double blind studies.

Selection criteria included absence of antimalarial treatment during the preceding two weeks, clinically manifest malaria due to mono-infection with *P. falciparum,* asexual parasite density of 1,000 – 100,000/µl blood, absence of signs of severity or complications.

While febrile, the body temperature was measured at 6-hourly intervals. After defervescence the intervals were increased to 12 hours. Similarly, parasite counts were done 6-hourly while parasitaemia was present. After two sequential negative readings, blood examinations were done daily until the end of the observation period.

In the parasitological evaluation of the treatment results the WHO classification of the extended in vivo thest was followed (2), generally based on 28 days of observation, except for sulfadoxine/pyrimethamine (42 days) and mefloquine (63 days) where the relatively long elimination half-life dictated an extended follow-up.

Patients with R-III responses received alternative treatment as soon as the R-III status became evident. Alternative treatment of R-II cases was effected after day 7, and in R-I cases after confirmation of the recrudescence.

Results

In the first observation series, between 1971 and 1977, chloroquine, sulfadoxine/pyrimethamine (S/P, Fansidar®) and quinine were evaluated (Tab. 1). There was evidence of substantial chloroquine resistance, both in frequency (96%) and degree (52% R-II/R-III), and of already

Table 1:

Treatment of falciparum malaria in adolescents in Thailand 1971 - 1977 (3)

Drug	Dose and Regimen	No. of Pat.	Result (%)			
			S	R-I	R-II	R-III
Chloroquine	Total 1500 mg in 4 doses over 3 days	25	4	44	28	24
S/P*	Single dose 1000 mg S + 50 mg P	30	77	17	7	–
S/P + Chloroquine	1000 mg S + 50 mg P as single dose + chloroquine total 1500 mg in 4 doses over 3 days	23	65	26	9	–
S/P + Quinine	1000 mg S + 50 mg P as single dose + quinine 500 mg 8-hourly for 3 days	31	68	29	3	–
S/P + Quinine	1000 mg S + 50 mg P as single dose + quinine 500 mg 8-hourly for 5 days	32	91	9	–	–

* S/P = Sulfadoxine + Pyrimethamine

Table 2:

Treatment of falciparum malaria in adolescents in Thailand 1980 (4)

Drug	Dose and Regimen	No. of Pat.	Result (%)			
			S	R-I	R-II	R-III
S/P*	Single dose 1000 mg S + 50 mg P	27	7	15	63	15
S/P	Single dose 1500 mg S + 75 mg P	18	11	39	39	11
S/P* + Quinine	100 mg S + 50 mg P as single dose + quinine 500 mg 8-hourly for 5 days	23	57	43	–	–

* S/P = Sulfadoxine + Pyrimethamine

reduced efficacy of S/P (23% R-I/R-II) which could not be improved by an association with chloroquine or a three day course of quinine. However, if S/P was complemented by a five day course of quinine, the cure rate improved significantly.

Subsequently the efficacy of S/P alone has rapidly dropped and by 1980 the cure rate had decreased to less than 10% (Tab. 2). There was no substantial improvement with the use of a larger dose, only a shift from R-II to R-I. Also the combination with a five day course of quinine had suffered a marked decrease of efficacy, indicative of simultaneously reduced quinine sensitivity of *P. falciparum*.

The outcome of treatment with quinine was shown to be related to the drug levels in the blood and the minimum inhibitory concentration (MIC) of quinine. In children who were given quinine 8-hourly at a dose of 10 mg/kg body weight, blood levels reached the peak on day 2 and than droped rapidly, after clinical normalization, towards the end of the first week. Treatment failure occurred in all patients where the quinine concentration could not be maintained above the MIC for at least seven days. A comparative study of a seven day regimen of 8-hourly administration of quinine 10 mg/kg, and a regimen with increased doses (15 mg/kg) from day five to day seven suggested that a seven day course is too short (Tab. 3).

Based on these results, an extended regimen was evaluated in 1986 to 1988, using quinine 8-hourly at 10 mg/kg for four days, followed by the 8-hourly administration of 15 mg/kg for another four days. The cure rate was substantially improved over the seven day regimen (Tab. 4), obviously due to a prolongation of the effective quinine blood levels. The extended regimen is particularly useful in children under seven years who cannot be given tetracycline.

In adults the combined seven day course of quinine and tetracycline is still quite effective in Thailand, yielding a cure rate of > 90% (6). While tetracycline exerts antimalarial activity on its own, it also increases the blood levels of quinine when given in combination (7).

Since tetracyclines are contraindicated in children below the age of seven years, an attempt was made to improve treatment results by the use of erythromycin which is acceptable

Table 3:

Treatment of falciparum malaria in children in Thailand 1981 (5)

Drug	Dose and Regimen	No. of Pat.	Result (%)			
			S	R-I	R-II	R-III
Quinine	10 mg base/kg 8-hourly for 7 days	28	75	21	4	—
Quinine	10 mg base/kg 8-hourly for 4 days followed by 15 mg base/kg 8-hourly for 3 days	26	62	38	—	—

Table 4:

Treatment of falciparum malaria in children in Thailand 1986 - 1988

Drug	Dose and Regimen	No. of Pat.	Result (%)			
			S	R-I	R-II	R-III
Quinine	10 mg base/kg 8-hourly for 4 days followed by 15 mg base/kg 8-hourly for 4 days	25	92	8	—	—
Quinine + Erythromycin	Quinine 10 mg base/kg 8-hourly + Erythromycin 10 mg/kg 8-hourly for 7 days	28	93	7	—	—

Table 5:

Treatment of falciparum malaria in children in Thailand 1982 - 1984 (8)

Drug	Dose and Regimen	No. of Pat.	Result (%)			
			S	R-I	R-II	R-III
Mefloquine	17 - 33 mg base/kg single or divided doses	82	98	2	—	—

in paediatric practice and known to have some blood schizontocidal effect on its own. A seven day combined course of quinine 10 mg/kg and erythromycin 10 mg/kg, both 8-hourly, proved to be as effective as the stepped-up eight day regimen with quinine (Tab. 4).

Extended regimens with quinine are sustainable under good and rigid clinical conditions, but rarely in the outpatient environment. Moreover, such regimens are associated with unpleasant side effects. Therefore mefloquine alone or combined with S/P was evaluated in children between 1982 and 1986 (Tab. 5 and 6). The cure rates exceeded 90% and were obviously dose-dependent. However, the efficacy of mefloquine and its combination with S/P started to decrease in the late 1980s, especially on the Thailand-Cambodia border (9).

The rapidity of the clinical activity of quinine suggested continued attention on the *Cinchona* alkaloids. A comparative study of seven day regimens of quinine and a combination of quinine, quinidine and cinchonine (1 : 1 : 1) showed better results with the combination at equal dose level. A marked and significant improvement of the cure rate to 97% was achieved by raising the dose level of the combination from 10 mg/kg to 12 mg/kg (Tab. 7).

Conclusions and outlook

Drug resistance of *P. falciparum* in Thailand is a major operational constraint of malaria control. However, in spite of the loss of chloroquine and S/P for the treatment of falciparum malaria, the annual mortality from malaria in Thailand has continued to decrease as to reach the lowest ever recorded level in 1992 (THIMASARN, K., personal communication). To a large part this was due to countrywide facilities for rapid diagnosis and effective treatment. Such treatment relies on continuous updating of drug regimens such as shown in this paper.

P. falciparum in the eastern and western border areas and the adjacent parts of Cambodia and Myanmar has shown a considerable ability of developing resistance as borne out by the substantial decrease of quinine sensitivity and the recent rise of mefloquine resistance. There-

Table 6:

Treatment of falciparum malaria with a fixed dose combination of mefloquine, sulfadoxine and pyrimethamine (MSP*) in children in Thailand 1986

Group	Mefloquine Dose mg base/kg		No. of Pat.	Response %)	
	Mean	Range		S	R-I
1	10.0 ± 1.7	7.1 – 12.5	33	91	9
2	15.7 ± 1.5	15.2 – 17.9	38	97	3
3	20.6 ± 1.7	18.1 – 23.0	19	95	5
4	27.1 ± 3.4	23.3 – 33.3	27	100	–

* MSP tablets contain 250 mg mephloquine base as hydrochloride, 500 mg sulfadoxide and 25 mg pyrimethamine.

Table 7:

Treatment of falciparum malaria in children in Thailand 1987 (10)

Drug	Dose and Regimen	No. of Pat.	Result (%)			
			S	R-I	R-II	R-III
Quinine	10 mg base/kg 8-hourly for 7 days	30	57	37	7	–
Falcimax*	10 mg base/kg 8-hourly for 7 days	30	70	30	–	–
Falcimax	12 mg base/kg 8-hourly for 7 days	30	97	3	–	–

* Falcimax TM = Quinine : Quinidine : Cinchonine (1 : 1 : 1)

fore the search for and evaluation of new antimalarial drugs is continuing. In this endeavour halofantrine was studied, both in adults and children, yielding a high cure rate (11, 12). However, recently it has been shown that the efficacy of the standard regimen of halofantrine is decreasing, possibly on account of cross-resistance with mefloquine (13).

Currently, attention is focused on artesunate and artemether, processed derivatives of artemisinin from *Artemisia annua*. These drugs were shown to be effective against falciparum malaria in Thailand (14). A total dose of 600 mg artesunate over five days combined with a total (divided) dose of 1,250 mg mefloquine in adults produced a cure rate of 100% (15). Among other new drugs under evaluation at the Hospital for Tropical Diseases are atovaquone (compound 566 C 80), a naphthoquinone, and its combination with proguanil.

Summary

Chloroquine resistance of *Plasmodium falciparum* occurred in Thailand in the late 1950s. Increasing drug resistance necessitated the systematic evaluation of alternative antimalarials and drug regimens in keeping with the aggravating drug response situation. Studies in children and adolescents are particularly important as thes age groups differ from adults in reect of pharmacokinetic and toxicological features. The paper describes the evolution of the drug response of *P. falciparum* in Thailand and the elaboration of appropriate drug regimens for adolescents and children over the past two decades, as well as the current therapeutic prospects under conditions of multiresistance.

Key words *Plasmodium falciparum,* Antimalarials, Chemotherapy, Drug Resistance, Paediatrics.

Zusammenfassung

Therapeutische Probleme bei resistenter Falciparum Malaria bei Kindern und Jugendlichen in Thailand

Chloroquinresistenz bei *Plasmodium falciparum* wurde in Thailand erstmals in den späten 1950er Jahren beobachtet. Zunehmende Resistenz machte die systematische Auswertung anderer Malariamittel erforderlich, um der sich zunehmend verschlechternden Lage gerecht zu werden. Derartigen Studien bei Kindern und Jugendlichen kommt besondere Bedeutung zu, da sich diese Altersgruppen hinsichtlich Pharmakokinetik und Arzneimittelverträglichkeit erheblich von Erwachsenen unterscheiden. Die Arbeit beschreibt die Entwicklung der Arzneimit-

telresistenz von *P. falciparum* in Thailand und die Prüfung geeigneter neuer Medikationen während der vergangenen zwei Jahrzehnte, sowie die gegenwärtigen therapeutischen Aussichten in einer von Multiresistenz geprägten Situation.

Schlüsselwörter *Plasmodium falciparum,* Malariamittel, Chemotherapie, Arzneimittelresistenz, Pädiatrie.

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