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Therapeutic efficacy of anti-malarials in *Plasmodium falciparum* malaria in an Indo-Myanmar border area of Arunachal Pradesh

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***Background & objectives*: Malaria is one of the major public health problems in the north eastern region of India. Antimalarial drug resistance is widespread and one of the important causes of recent resurgence of falciparum malaria in this region. Antimalarial drugs are seen to be used sequentially one after another in many areas of the region, when therapeutic failure is observed with a drug. In view of this, the present study was undertaken to assess the therapeutic efficacy of common antimalarial drugs *viz.*, chloroquine, sulfadoxine+pyrimethamine (S-P) and quinine, administered sequentially to the patients with *Plasmodium falciparum* infection in a Myanmar bordering area of Arunachal Pradesh.**

***Methods*: A hospital based *in vivo* study was carried out with 53 patients with uncomplicated falciparum malaria. All patients were first treated with chloroquine and therapeutic efficacy assessed. In case of therapeutic failure of chloroquine combination drug (S-P) was given and those showing failure with S-P combination, oral quinine was administered and followed up for 28 days to assess both clinical and parasitological responses.**

***Results*: Therapeutic failure was observed with chloroquine in 83.1 per cent (44 of 53) and to both chloroquine and S-P combination drug in 44.1 per cent (19/43) patients. Further, 15.8 per cent patients (3 of 19) failed to respond even to quinine. Overall, 5.7 per cent patients (3 of 53) showed unresponsiveness to all the three drugs *i.e.*, chloroquine, S-P combination and quinine. Asexual parasite clearance and also fever clearance was slowest with chloroquine and fastest with quinine.**

***Interpretation & conclusion*: The findings of this study show the presence of multi drug failure *P. falciparum* in Jairampur-Nampong, a western Myanmar bordering area of Arunachal Pradesh. Anti malarial drug resistance is increasing in Indo-Myanmar border areas and systematic studies need to be done to review the situation.**

Key words Chloroquine - falciparum malaria - Indo-Myanmar border - *in vivo* resistance - north east India - sulfadoxine+pyrimethamine - therapeutic failure

The development and spread of drug resistant falciparum malaria has been identified as a key factor in the resurgence of malaria and one of the greatest challenges to malaria control today[1]. Various factors relating to drug, parasite and human host interactions contribute to the development and spread of drug resistance[2]. Chloroquine resistance to *Plasmodium falciparum* (Pf) appeared more or less simultaneously during 1960 in Colombia (Latin America) and Thailand (Southeast Asia) following which resistant Pf strains, not only to chloroquine but also to other antimalarial drugs like sulfadoxine+pyrimethamine (S-P) combination, mefloquine and quinine, have been detected in most countries of Southeast Asia region[3]. In India, the

chloroquine resistant Pf first detected from Manja primary health centre area of Assam in north eastern region of India (NE India) in 1973[4], is widespread in all the seven states of NE India as well as other parts of the country[5]. Resistance to S-P combination drugs and reduced efficacy to quinine has also been reported[5,6] from many areas of NE India that shares a long international border of about 3600 km with Bhutan, China, Myanmar and Bangladesh. This region is highly vulnerable for the importation of resistant strains from neighbouring countries, particularly Myanmar where high degree of Pf resistance to chloroquine, S-P combination drugs and mefloquine has been reported from its western parts bordering NE India[7]. Chloroquine is still the first line of treatment for malaria in most parts of NE India. However, in many chloroquine resistant areas, the alternate drug schedule has been introduced by Indian National Anti Malaria Programme (NAMP) which envisages treatment of fever cases with chloroquine presumptively and administration of S-P combination drug or quinine (if S-P combination fails) to microscopically confirmed Pf cases[8] practically ending up in sequential treatment of falciparum malaria cases with chloroquine, S-P combination drug and quinine. Jairampur-Nampong area of district Changlang in Arunachal Pradesh is a Myanmar bordering area where high degree of chloroquine resistance to Pf was detected in 1982. Resistance to S-P combination drugs was also recorded in adjoining areas of Jairampur-Nampong in the year 1992. Subsequently in 1995 this area was brought under the alternate drug schedule of NAMP, India[5]. Recently, a case of Pf malaria concurrently resistant to chloroquine and S-P combination drug was reported from Arunachal Pradesh raising concern about the possibility of emergence of multi drug resistance in Pf in NE India[9]. Therefore, to assess the present status of therapeutic efficacy of common antimalarial drugs for the treatment of falciparum malaria, particularly the extent of multi drug failure, the present study was carried out in Jairampur-Nampong area of Arunachal Pradesh state, India.

Material & Methods

Study area: The study was carried out in the Government Hospital, Jairampur (27°18'N, 95°57'E), Changlang district, Arunachal Pradesh, India located at a distance of about 15 km from the western border of Myanmar. Jairampur-Nampong area with about 35,000 population is historically endemic for falciparum malaria with an average annual parasite incidence of 25-50 per thousand population[10]. People mainly belonging to Tangsa ethnic group (>80%) reside on both the sides of Indo-Myanmar border and have subsistence farming as the main source of livelihood. This area is under alternate drug (S-P combination) schedule of NAMP, India since 1995.

Study subjects: The patients were selected among the out door patients attending Jairampur hospital during 1999. Patients above 1 yr of age, presenting with acute fever or history of fever during the preceding 24 h, along with microscopically confirmed *P. falciparum* mono-infection having asexual parasite count between 1000-100,000/µl without severe anaemia, as assessed by clinical examination, were selected for the study after obtaining written informed consent either from the patient (adult) or from the parents or guardians in case of minors. Patients having signs and symptoms of severe malaria[11] or danger signs as per WHO criteria[12] or those with severe malnutrition or with any other concurrent infection or disease or with known history of sulfonamide drug sensitivity or having potential problem of follow up were excluded from the study. Women with history of missed periods were also excluded.

The study was approved by the Ethics Committee of the Regional Medical Research Centre, (ICMR) Dibrugarh, India.

Clinical and parasitological examination: At the time of enrollment a thorough physical examination of all patients was done and blood was collected for smears (thick & thin) after finger pricking in Jairampur hospital. Axillary temperature was recorded with a standardized digital thermometer. Blood slides were examined after staining with 3 per cent Giemsa for 30 min. Asexual parasites were counted against 300 leukocytes. The parasite density was expressed as the number of asexual parasites/µl blood by assuming a mean normal leukocyte count of 8000/µl.

Treatment regimen: All patients were given chloroquine (25 mg/kg body weight) in 3 days (Day 0-10 mg, D1-10 mg, D2-5 mg) orally under direct supervision. Patients were monitored for vomiting, for about an hour, after

administering the first dose of the drug. A replacement dose was given, if necessary. Those patients who vomited out the first as well as replacement dose of the drug were not included in the study and were treated with i.v. quinine in 5 per cent dextrose. Patients showing therapeutic failure to chloroquine in absence of signs and symptoms of complicated Pf malaria or danger signs were administered single oral dose of sulfadoxine (25 mg/kg body weight) + pyrimethamine (1.25 mg/kg body weight). Further, patients showing treatment failure to both chloroquine and S-P combination drug in absence of complications or danger signs or signs of toxicity were administered oral quinine (10 mg/kg body weight) three times a day for a period of 5 to 7 days, depending on the compliance and tolerance. Patients showing failure even to quinine were treated with mefloquine (15 mg/kg body weight) single dose.

The antimalarial drugs used in the study were in good condition and procured from NAMP, Guwahati office except that of mefloquine that was used after procuring from the open market as this drug is not supplied by the NAMP.

Parasitological and clinical response monitoring: Chloroquine was given to the patients in the outpatient department and after one hour of monitoring patients were allowed to go home. However, patients were admitted in the Government hospital, Jairampur for a period of 7 days during the treatment with S-P combination drug or quinine for close monitoring. Any patient developing signs and symptoms of complication, danger or toxicity sign was withdrawn from the study and alternate treatment was given. All patients were followed up for a period of 28 days after the treatment.

Monitoring of therapeutic efficacy was carried out using the modified WHO protocol, 1996[12]. Both thick and thin blood smears as well as axillary temperature was recorded on days 0, 2, 3, 7, 14, 21 and 28 in patients treated with chloroquine and cases successively treated with S-P combination drug (showing failure to chloroquine) and quinine (showing failure to both chloroquine and S-P combination drugs).

The clinical responses were classified as follows (*i*) early treatment failure (ETF) : if the patient developed danger signs or severe malaria on or before day 3 in the presence of asexual parasitaemia or when parasitaemia on day 2 was higher than day 0 count irrespective of axillary temperature or when parasitaemia on day 3 was present with axillary temperature ≥ 37.5°C or when parasitaemia on day 3 was ≥ 25 per cent of the count on day 0, (*ii*) late treatment failure (LTF): development of danger signs or severe malaria after day 3 or presence

Table I. Characteristics of patients enrolled in therapeutic response study

Category		Chloroquine*	S-P combination drug**	
				Quinine***
No. of patients		53	43	19
Sex	Male	38	30	15
	Female	15	13	4
Age (yr)	Mean±SD	20.2±13.4	19.8±13.2	21.4±12.9
	(range)	(2.5-55)	(2.6-55)	(4.5-49)
	Median	16.0	14.0	11.0
Weight	Mean±SD	39.6±14.8	39.1±15.2	41.1±14.3
(kg)	(range)	(12-65)	(13-65)	(20-60)
Ethnicity	Tribal	30	26	13
	Non-tribal	23	17	6

*All patients initially selected for the study were given chloroquine, **Chloroquine failure cases were treated S-P combination drug along with primaquine, ***Chloroquine and S-P combination drug failure cases were treated with quinine

of parasitaemia and axillary temperature ≥ 37.5°C between day 4-28 or presence of parasitaemia between day 7-28, irrespective of axillary temperature ≥ 37.5°C and (*iii*) adequate clinical and parasitological response (ACPR): absence of parasitaemia on day 28, irrespective of axillary temperature, without previously meeting any criteria of ETF or LTF.

Data analysis: The data were analyzed using EPI-Info version 6.04d (Centres for Disease Control and Prevention, Atlanta, USA). Geometrical means of parasite density were calculated for persons with detectable parasitaemia. Proportions were compared by Chi square text.

Results

A total of 891 patients with fever were screened for malaria during the study period, of whom 265 were found malaria positive [Pf-190, *P. vivax*, (Pv)-71, mixed (Pv+Pf)-4]. Of these, a total of 58 consecutive patients positive for Pf, satisfying the inclusion criteria, were enrolled in the study. Fifty three patients completed the chloroquine study (Table I) while 5 were lost to follow up. In case of chloroquine, ACPR was found only in 9 (17%) patients; ETF and LTF together (n=44) gave a failure rate of 83.1 per cent (Table II). Of the 44 patients with chloroquine failure, one developed signs of cerebral malaria on day 3 and was withdrawn from the study and treated with quinine i.v. in 5 per cent dextrose. The remaining 43 were treated with S-P combination drug. On follow up, 24 patients (55.9%) showed adequate clinical and parasitological response whereas 19 (44.1%) showed therapeutic failure at various levels to S-P combination drug (Table II). These 19 patients were administered oral quinine, only 8 could complete the full 7 days course of quinine while 11 patients could not continue beyond 5 days having developed tinnitus, dizziness and gastritis (n=7), nausea and vomiting (n=3) on day 5, one patient refused to take quinine after day 5. Tinnitus was developed in two patients who completed the 7 days treatment. In 5 days quinine treatment group, reduction in asexual parasitaemia was 20 per cent in two patients on day 3 as compared to day 0. However, on day 7 both became asymptomatic but their asexual parasite count was >25 per cent of the day 0 count. In 7 days quinine treatment group, only 1 failure at ETF level was recorded both on days 3 and 7. Thus, the overall failure rate of quinine was 15.8 per cent (3 out of 19) in the study that was slightly higher (18.1%) in 5 days treatment group than in 7 days treatment group (12.5%). The 3 patients showing therapeutic failure to chloroquine, S-P combination drug and quinine were treated with mefloquine and their follow up for next 28 days showed sensitivity to this drug. Overall, 83.1 per cent patients were non-responsive to chloroquine alone, 35.8 per cent failed to chloroquine and S-P combination both and in 5.7 per cent therapeutic failure to chloroquine, S-P combination and quinine was noted.

The rate of asexual parasite clearance in patients on different days of follow up was slowest with chloroquine and fastest with quinine. The drop in parasitaemia after 2 days of treatment was about 32, 62 and 70 per cent in chloroquine, S-P combination drug and quinine respectively. After 2 days of treatment only 26.4 per cent patients were found parasitaemic in case of quinine as compared to 67.4 and 98.1 per cent in S-P combination drug and chloroquine respectively ($P<0.000$). On day 7, the proportion of parasitaemic patients was 15.8, 17.2 and 47.6 per cent in quinine, S-P combination and chloroquine treatment cases respectively ($P<0.02$). The pattern of fever clearance in the three groups was more or less similar to that of parasite clearance on different days of follow up. However, in patients treated with S-P combination drug a slight rise in axillary temperature on days 2 and 3 was recorded after a drop in temperature on day 1.

Discussion

Though the evolution and spread of drug resistance is not fully understood it is postulated that chloroquine resistance in Asia was originated from a single focus in the Cambodian area of Paillang near Thai border and from there it spread to the surrounding areas[13]. International border areas are particularly vulnerable for importation and precipitation of drug resistant malaria requiring special attention. In the Jairampur area chloroquine resistance to the tune of 90 per cent with about 60 per cent cases being RI type and 30 per cent RII and RIII type (as per old WHO classification) was detected[5]. In the present study though total failure rate of chloroquine was nearly the same *i.e.*, about 83 per cent, the ETF (approximately equivalent to RII and RIII resistance together) was about 60 per cent indicating consolidation and stabilization of chloroquine resistance during the intervening period. Similarly, the level of resistance to S-P combination drug (5.3%) as found in

Table II. Therapeutic response of chloroquine and S-P combination drug

Category	Drug	Characteristic	Total	ETF (%)	LTF (%)	ACPR (%)	Total failure (%)
No of cases	CHQ		53	32	12	9	44
				(60.4)	(22.6)	(17.0)	(83.0)
	SP		43	14	5	24	19
				(32.6)	(11.6)	(55.8)	(44.2)
Age group	CHQ	≤15 yr	25	16	5	4	21
		>15 yr		(64.0)	(20.0)	(16.0)	(84.0)
			28	16	7	5	23
				(57.1)	(25.0)	(17.9)	(82.1)
	SP	≤15 yr	20	5	3	12	8
				(25.0)	(15.0)	(60.0)	(40.0)
		>15 yr	23	9	2	12	11
				(39.1)	(8.7)	(52.2)	(47.8)
Sex	CHQ	Male	38	23	4	8	30
				(60.5)	(10.5)	(21.2)	78.9)
		Female	15	9	5	1	14
				(60.0)	(33.3)	(6.7)	(93.3)
	SP	Male	30	12	4	14	16
				(40.0)	(13.3)	(46.7)	(53.3)
		Female	13	2	1	10	3
				(15.4)	(7.7)	(76.9)	(23.1)
Ethnicity	CHQ	Tribal	30	20	5	5	25
				(66.7)	(16.7)	(16.7)	(83.3)
		Non-tribal	23	12	7	4	19
				(52.2)	(30.4)	(17.4)	82.6)
	SP	Tribal	26	10	3	13	13
				(38.5)	(11.5)	(50.0)	(50.0)
		Non-tribal	17	4	2	11	6
				(23.5)	(11.8)	(64.7)	(35.3)
Geometric mean of asexual parasitaemia (per µl of blood)	CHQ	Day 0 value	5345	7745	4803	2879	
	SP	Day 0 value	3729	3876	4260	3521	

CHQ - chloroquine treated patients; S-P - patients treated with sulfadoxine + pyremethamine combination drugs showing failure to chloroquine treatment; ETF - Early treatment failure; LTF - Late treatment failure; ACPR - Adequate clinical and parasitological response

1992[5] also seems to have gone up substantially to about 44 per cent therapeutic failure to S-P combination drug in this study. Thus, within 4 yr of introduction of the revised drug policy of NAMP (1995), S-P combination drug in Jairampur-Nampong area has lost its effectiveness to a great extent. Another disturbing aspect is the persistence of parasitaemia up to day 3 in 15 per cent cases treated by quinine after treatment failure with

both chloroquine and S-P combination drug. The plausible reasons for such a fast development of antimalarial drug resistance in Jairampur-Nampong area could be the high drug pressure in the presence of intense transmission, particularly by *Anopheles dirus* (considered well adapted to drug resistant Pf strains) and frequent population movement across Indo-Myanmar border. These factors were considered as most favourable for disseminating drug resistant Pf malaria from Thai-Kampuchea border to other Southeast Asian countries[14].

As this study was limited to only one site, it is difficult to make any generalization. Nevertheless, the present study unequivocally establishes the presence of strains of *P. falciparum* concurrently non-responsive to chloroquine, S-P combination drug and quinine in Myanmar bordering areas of Arunachal Pradesh. Though quinine, at present, appears to be a satisfactory drug for the treatment of Pf positive cases in this area, poor compliance due to the potential toxicity of oral quinine is a limiting factor in fully utilizing its potential to treat uncomplicated falciparum cases. Moreover, its use should be limited for the treatment of complicated cases of falciparum malaria only. Exploratory research is needed to enhance the effectiveness of S-P combination drug and appropriate steps to delay the spread and further consolidation of its resistance. Roll back malaria initiative of WHO has emphasized on combination therapy as a tool to enhance the effective life of an antimalaria[15]. Further, there is a need for a review of present drug policy in border areas having the problem of multi drug resistant *P. falciparum* malaria.

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