THE DRUG SENSITIVITIES OF *PLASMODIUM FALCIPARUM* IN THE SONITPUR DISTRICT, ASSAM, INDIA

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Abstract. Falciparum malaria is an ongoing problem in the foothills of Northeast India. Evaluation of the drug sensitivities of *P. falciparum* was carried out in four endemic villages of the Sonitpur District of Assam, involving 218 cases who were tested *in vivo* over 35 days. Chloroquine resistance was detected at the RI level in 29 cases (13%) and RII level in 8 cases (4%). No RIII chloroquine resistant cases were detected in the study. RI resistance was observed in the age groups 6-10 years, 11-14 years, and 15 years and above in 16%, 17%, and 13%, respectively. RII level resistance was observed in 4% of all those groups combined. All the RI and RII resistant cases responded well to a single dosage of Metakelfin (sulfamethoxypyrazine I.P 1,500 mg and pyrimethamine I.P 75 mg).

INTRODUCTION

The endemicity of malaria in the foothills of Northeast India has been known for decades. Sporadic outbreaks occur during the rainy season in certain pockets of rural and forested areas. During the transmission season, the slide positivity rate (SPR) ranges between 35 and 46%, with 60-80% being *Plasmodium falciparum* cases (Bhuyan *et al*, 1997; Kamal and Das, 2001). Prompt and effective treatment of all cases is a well-accepted fundamental component of the global strategy for malaria control. Chloroquine resistant *P. falciparum* poses a major challenge to proper treatment and management of malaria cases. The problem becomes further complicated when drug resistance coexists with vector resistance to insecticides. It has been observed that quinine has been indiscriminately used for the treatment of uncomplicated malaria due to the lack of data on the drug sensitivities of *Plasmodium falciparum* in this region. Chloroquine resistance has been reported from different parts of the world and resistance to quinine has been observed in Thailand and Vietnam (WHO,1987). In India, chloroquine resistance was first reported from Diphu (Karbi Anglong District), Assam during the seventies (Sehgal *et al*, 1973) and subsequently several foci have been detected in Arunachal Pradesh, Mizoram, Nagaland and Meghalaya in the northeastern region. (Das *et al*, 1979; Pattanayak *et al*, 1979; Borkakati *et al*, 1984).

A study was planned to conduct a trial of the sensitivity of *P. falciparum* to chloroquine in 2000-2001, in four villages under Dhekiajuli PHC of the Sonitpur District, Assam, India. The findings of the investigation are being communicated in this paper.

MATERIALS AND METHODS

Study area

District Sonitpur lies in the northern part of Assam, sharing a border with Arunachal Pradesh (Longitude 92º 20′E to 93º 45′E and Latitude 26º 20′N to 27º 05′N). Four villages (Ramnathpur, Belsiri Nonke, Nagapathar, and Missamari) with a population of 14,511 under Dhekiajuli PHC were selected for the study. The villages were located on the fringe of an evergreen rain forest in the foothills of Assam along the Arunachal Pradesh border. A mixed population comprised of Assamese, Nepalese, Tea garden laborers and Bodo tribes mainly inhabit the area. Paddy cultivation and daily wage agricultural labor is the prime livelihood of the village inhabitants. Temperature and relative humidity range between 26.7º-29.9ºC and 66.2-87.6% in the summer and 18.1º-26.2ºC and 73.6-82.9% in winter, respectively. Total rainfall during the rainy season ranges between 1,162.8 mm and 1,803.9 mm.

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Active surveillance and mass blood surveys were carried out in the villages to detect malaria cases. Both thick and thin blood films were obtained. Giemsa stained thick blood films were used for parasite counts and thin blood films were used for species identification. The number of asexual stages per 400 white blood cells was counted and multiplied by 20 to give an estimated count per μl of blood. A minimum parasitemia of 500 asexual parasites per μl was selected for the study. All complicated cases and those with a history of taking antimalarials within the previous fortnight were excluded. Patients suffering from uncomplicated malaria with *P. falciparum* infection were treated without hospitalization with a chloroquine base dose 25 mg/kg of body weight in three divided dosages for three days, as recommended by the WHO/NMEP schedule. Follow-up blood samples were collected from treated patients every seven days for 35 days with close observation for the first 7 days, as per the WHO extended drug sensitivity field test procedure. Patients were included in the final assessment only if their follow-up examination had been completed to day 35. In cases where parasitemia reappeared (recrudescence) within 35 days, they were treated with a single dose of sulfamethopyrazine I.P. 1500 mg and pyrimethamine I.P. 75 mg (Metakelfin). The patient took the drugs under medical supervision.

RESULTS

A total of 769 blood samples were collected from 4 villages during the period. Out of these, 352 (45.8%) samples were positive for malaria parasites. *P. falciparum* infection was detected in 350 (99.4%) (Table 1). Altogether, 218 *P. falciparum* cases were successfully followed for 35 days after treatment with chloroquine. On completion of the trial, 181 (83%) were found to be sensitive to chloroquine, as no clinical symptoms or recrudescence of the *P. falciparum* parasite were observed in the blood samples of the patients for 35 days. Tolerance to chloroquine was observed in the parasites of 37 patients (17%) (Table 2). Those cases were further classified into three categories. In 9 cases, early R1 resistance occurred where the parasite reap-

Table 1
Malaria incidence among different age groups in villages under Dhekiajuli PHC of Sonitpur district, Assam, India.

Age group	BSC	Positive	SPR	Pf	Pf%
1-5	120	30	25.0	29	96.7
6-10	199	108	54.3	108	100.0
11-14	195	106	54.4	105	99.1
>15	255	108	42.4	108	100.0
Total	769	352	45.8	350	99.4

Table 2
Results of drug sensitivity trial.

Drug	Pf cases	Sensitive	RI	RII	RIII
Chloroquine 25 mg/kg body wt	218	181 (83%)	29(13%)	8 (4%)	-
Metakelfin 1,500 mg +75 mg adult	37	37 (100%)	-	-	-

Table 3
Asexual parasite count/μl of blood at different intervals.

Malaria cases	Day 0	D 7	D 14	D 21	D 28	D 35	Degree of resistance
181	660-15,860	Neg	Neg	Neg	Neg	Neg	Susceptible
9	1,240-20,360	Neg	540-10,280	-	-	-	RI Early resistance
20	9,580-17,740	Neg	Neg	3,680-9,880	-	-	RI Delayed resistance
8	840-23,300	360-5,240	920-13,800	-	-	-	RII Resistance

Table 4
Chloroquine sensitivity among different age groups.

Drug	Age group	Pf case	S No (%)	RI No (%)	RII No (%)	RIII
Chloroquine 25 mg/kg body wt	1-5	25	25 (100)	-	-	-
	6-10	70	56 (80)	11(16)	3 (4)	-
	11-14	48	38 (78)	8 (17)	2 (4)	-
	>15	75	62(83)	10 (13)	3 (4)	-
Total		218	181 (83)	29 (13)	8 (4)	

peared between days 7 and 14. In 20 cases, delayed RI resistance occurred in parasites between days 21 and 28. Eight cases were identified as having RII levels of resistance, where the parasitemia decreased substantially during the first week, but did not disappear. RIII cases (no marginal decrease in parasitemia) were not found in our study (Table 3). Both the RI and RII resistant cases responded well to Metakelfin.

The age group of 1-5 years exhibited 100% chloroquine sensitivity. RI level resistance was observed in the age groups of 6-10 years, 11-14 years, and 15 years and above in 16%, 17%, and 13%, respectively. RII level resistance was observed in 4% of all the groups from age 6 to 15 years and above (Table 4).

DISCUSSION

Sehgal *et al* (1973) reported RI resistance in 52.5% and RII in 22.5% of cases of *P. falciparum* infections in Assam. In another study, Sehgal *et al* (1974) reported RI resistance in 24% of cases from a group of 6 tea estates in the Nowgong District. Pandya *et al* (1990) recorded RI, RII, and RIII resistance in 34.8%, 6.6%, and 4.8%, respectively, during 1986-1988 in 227 cases from Assam. In our study, RI (RI early+ RI delayed) and RII resistance were recorded only in 13% and 4%, respectively. Similar observations by Gogoi *et al* (1995) were made from adjacent tea estates in Tarajuli and Paneri. In both these studies, no RIII chloroquine resistance was reported, contrary to Sehgal *et al* (1973). The differences in the degree of resistance may be due to variation in the strains and/or differential drug pressure as reported by Singh and Sukla, (1990). Premji *et al* (1999), reported 57% chloroquine sensitivity in children age 6 months to 5 years in the United Republic of Tanzania. In contrast to this, 100% chloroquine sensitivity was observed in children 1-5 years in our study. Resistant cases (RI+RII) appeared in the groups 6-10 years, 11-14 years and >15 years in 20, 20.8 and 17% respectively. Singh and Sukla (1990) observed no significant difference in resistance between children and adults to chloroquine administration at a tribal village in Madhya Pradesh, and recorded 12-22% resistance. Chloroquine resistant *P. falciparum* is gradually increasing, with most of the resistance being RI (Borkakati *et al*, 1984). This was confirmed by our study

(Table 1). A previous study showed that 40% of *P. falciparum* had resistance to chloroquine, showing mostly RI resistance. The sulpha-pyrimethamine combination drug worked well in all those resistant cases (Dua *et al* 1997). Similar observations were made in our study, where all the resistant cases responded well to Metakelfin.

The high proportion of chloroquine resistance and the predominance of RI resistance indicates the immune competence of the host population (Singh and Sukla, 1990). The administration of drugs in inadequate dosage schedules, as recorded in the present study, can enhance the process of natural selection for resistance in those locations.

Metakelfin (sulphalene and pyrimethamine) can be recommended as the drug of choice in treating resistance out-patient cases in this area, (advised by PHC medical officers). However, this drug must be employed judiciously as resistance to this drug has already been reported in India (Choudhury *et al,* 1987).

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REFERENCES

Bhuyan M, Das NG, Chakraborty BC, *et al*. Role of *Anopheles culicifacies* during an outbreak of malaria in Garubandha PHC Assam. *J Commun Dis* 1997; 29: 243- 6.

Borkakati BN, Kalita, PC Das, S Talukdar AC. Chloroquine resistant P. falciparum malaria in Assam and Meghalaya. *Indian J Malariol* 1984; 21: 55-6.

Choudhury DS, Sinha S, Ghose SK, Usha DC, Sharma VP. Report of a case of *Plasmodium falciparum* resistance to Chloroquine and combination of Sulphalene and pyrimethamine in Delhi. *Indian J Malariol* 1987; 24: 95-6.

Das S, Roy RG, Pattanayak S. A note on chloroquine resistance test on *P. falciparum* in Nagaland. *Indian J Med Res* 1979; 70 (suppl): 30-3.

Dua KV, Kar PK, Gupta NC, Kar I, Sharma VP. *In vivo* and *in vitro* sensitivity of *Plasmodium falciparum* to chloroquine in Chennai (Tamilnadu), India. *Indian J Malariol* 1997; 34: 1-7.

Gogoi SC, Dev V, Chaudhury B, Phookan S. Susceptibility of *Plasmodium falciparum* to chloroquine in Tea garden tribes of Assam, India. *Southeast Asian J Trop Med Public Health* 1995; 26: 228-30.

Kamal S, Das SC. Epidemiological observations on malaria in some parts of Darrang district, Assam. *Indian J Malariol* 2001; 38: 25-31.

Pandya AP, Borkakati BN, Narasimham MVVL, Mahapatra PK. *Plasmodium falciparum*- chloroquine *in vivo* test in Northeast India: Reclassification and extended follow up till day 14. *Indian J Malariol 1*990; 27: 223-9.

Pattanayak S, Roy RG, Sen S. Response to chloroquine with and without pyrimethamine in *Plasmodium falciparum* in West Bengal, Tripura, Mizoram, Manipur and Arunachal Pradesh. *Indian J Med Res* 1979; 70: 48.

Premji Z, Makwaya C Minjas JN. Current clinical efficacy of chloroquine for the treatment of *Plasmodium falciparum* infections in urban Dar es Salaam, United Republic of Tanzania. *Bull WHO* 1999; 77: 740-3.

Sehgal PN, Sharma MID, Sharma SL Gogoi S. Resistance to Chloroquine in *falciparum* malaria in Assam state. *J Commun Dis* 1973; 5: 175-80.

Sehgal PN, Sharma SL, Borkakaty BN. Efficacy of quinine with pyrimethamine against chloroquine resistance *Plasmodium falciparum* in Assam state India. *J Commun Dis*1974; 6: 260- 4.

Singh N, Sukla MM. Response of *Plasmodium falciparum* to chloroquine in a tribal area of Madhya Pradesh. *Indian J Malariol* 1990; 27: 183-6.

World Health Organization, The epidemiology of drug resistance of malaria parasites. Memorandum from a WHO meeting. *Bull WHO* 1987; 65: 797-816.