EFFECTIVENESS OF α–β ARTEETHER IN CLEARING *PLASMODIUM FALCIPARUM* PARASITEMIA IN CENTRAL INDIA (MADHYA PRADESH)

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Abstract Forty-six patients (25 Females + 21 Males) of uncomplicated *Plasmodium falciparum* in districts Jabalpur and Mandla of central India (Madhya Pradesh) were administered α–β arteether (an ethyl derivative of qinghaosu), intramuscularly for 3 consecutive days (150 mg once a day). The results revealed that there was rapid control of fever in all the patients without administration of any antipyretic drug. The mean parasite clearance time was 30.78 ± 10.92 hours and recrudescence/reinfection rate was 6.7% within 28 days. Study indicates that arteether, besides being a potent and fast acting schizontocidal drug, also exhibited gametocytocidal action on *P. falciparum*.

INTRODUCTION

The emergence of strains of *Plasmodium falciparum* resistant to chloroquine and other widely used antimalarials and the development of insecticide resistance by mosquitos have created serious problem in the control of malaria (Sharma, 1996). This has necessitated the search of alternative drugs for the treatment of this infection. The Central Drug Research Institute (CDRI), Lucknow had undertaken a multicentric clinical trial of α–β arteether all over India at 9 places with the aim of evaluating the efficacy of α–β arteether (Asthana *et al*, 1997). Clinical trial carried out at Government Medical College, Jabalpur have confirmed the antimalarial efficacy of arteether in the treatment of uncomplicated falciparum malaria cases (Khapra, 1996). We report here the effect of α–β arteether in clearing parasites in uncomplicated *P. falciparum* cases in two areas of different endemicity, terrain, socio-cultural practices and ethnic populations.

MATERIALS AND METHODS

Study area

The present study was also a part of multicentric Phase III clinical trial of α–β arteether (a new ethyl derivative of artemisinin developed at CDRI). The study was carried out in collaboration with Department of Medicine, Medical College, Jabalpur and in field in the tribal villages of district Mandla where malaria is perennial (Singh *et al*, 1997). The study was initiated in August 95 and completed in February 1996.

District Jabalpur is located in the center of Indian subcontinent, the endemic falciparum malaria zone of India. It is an important city of central India with 10,164 km² area and 2.6 million population. Government Medical College is the largest medical facility in the district and serves both as a hospital for local people and as a referral hospital for the division comprising of six districts. Urban slums are common in the city. The description of study area and its population have been described earlier (Shukla *et al*, 1995). Mandla, a tribal district, is just adjacent to Jabalpur. The study villages are thinly populated, scattered and drained by many parennial streams and their tributaries. The inhabitants are mostly tribals (95%) who are illiterate, health ignorant and very poor. The details of topographical and ecological features have been described earlier (Singh *et al*, 1997).

Study group

Patients with clinical malaria showing presence of asexual stages of *P. falciparum* in the peripheral blood, were selected for the study. Patients with

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severe and complicated malaria or who had history of taking antimalarials as confirmed by the presence of 4-amino quinoline or its degraded products in urine by standard text were excluded. Pregnant women and patients below 15 years were also not included in the study. Written informed consent was obtained from each patients. Arteether (150 mg) were administered intramuscularly once a day on three consecutive days. Three patients were administered only two injections of arteether as they left hospital without permission. They were also excluded from the study. Patients in Jabalpur were kept in Medical College Hospital for a minimum of 4 days or more if needed. In Mandla, the hospital admission of patients was not possible due to limited facilities at the Primary Health Center. Further followup of patients was done on day 7, 14, 21 and on day 28 by visiting their houses at both the places. Parasite counts were performed on days 0, 1, 2, 3, 7, 14, 21 and 28 using thick blood films stained with Giemsa stain.

Parasite count in each slide was done against 300 white blood cells following WHO procedure (WHO, 1987). Parasite clearance time (PCT) was defined as the time for asexual parasite to be cleared and to remain so upto day 7. Fever clearance time (FCT) was the time for the temperature to return to normal (37°C or 98.4°F) and remained so for atleast 48 hours. Patients were considered to be cured if no recrudescence occurred within this 28 day period.

RESULTS AND DISCUSSION

Data from 46 patients (25 females and 21 males) were analyzed separately for Jabalpur and Mandla (Table 1). The mean age was 31.6 ± 12.75 years (range 15-60 years). All patients had fever at the time of admission into this study with or without chill. The body temperature ranged from 99.0°F to 104°F (101.48 ± 1.38°F). There was rapid control of fever in patients treated with arteether without administration of any antipyretic drugs. In all 25 patients (54.35%) became afebrile within 24 hours of starting therapy, 14 (30.43%), and 6 patients (13.0%) became afebrile within 48 and 72 hours respectively, and only 1 patient (2.17%) remained febrile after 3 injection but became afebrile within 96 hours. Mean fever clearance time (MFCT) was 35.67 ± 18.39 hours.

The initial mean parasite count ranged from 114 to 74,322 mm^3 (7,502.04 ± 13,378.11). There was a rapid parasite clearance with arteether. Out of 46 patients, 33 (71.74%) became aparasitemic after first injection and remaining 13 patients (28.26%) were cleared of parasitemia with second injection. In no case asexual parasites were detectable in the blood smear on day 2. Even the patient who remained febrile after 3 injections had no parasitemia on day 2. Mean parasite clearance time (MPCT) was 30.78 ± 10.92 hours. In similar studies in Assam (Mohapatra *et al*, 1996) and Delhi (Valecha *et al*, 1997), MPCT were respectively 37.6 ± 13.6 hours and 19.94 ± 6.87 hours. These results are in line with those of Mishra *et al*, (1995) in Rourkela.

After 3 injections of arteether, gametocytes were seen in 19 cases (41.3%). These gametocytes became cleared within a week in 17 cases (36.9%) and persisted more than 14 days in 2 cases (4.34%). Similar observations of gametocytocidal action of artemisinin and its derivatives have been recorded in an *in vivo* study from China (Chen *et al*, 1994) and in India (Mohapatra *et al*, 1996).

Follow up of only 30 cases out of 46 revealed that seven patients did complain about fever during followup and all other patients were found to be asymptomatic up to 28 days. Blood smear was found positive for asexual stages of Pf again on day 21 (904 mm^3) in 1 patient of Jabalpur and on day 28 in another patient of Mandla (22,282 mm^3). Thus the study showed that MFCT and MPCT were similar in 2 groups and so is the reappearance of parasitemia within 28 days. Assuming them to be the cases of recrudescence, the recrudescence rate in our study worked out to be 6.7% which is very similar to Mohapatra *et al* (1996) in Assam and Valecha *et al* (1997) in Delhi, while Mishra *et al* (1995) recorded a relatively higher recrudescence rate (14%) in Rourkela.

Drug resistance to Pf malaria is quite common in central India (Houghton, 1983; Ghosh *et al*; 1989; Singh *et al*, 1989; Singh and Shukla, 1990). Recent studies in Mandla revealed that chloroquine is sensitive to only 45% cases and about 35% cases were resistant to RII-RIII type (Singh *et al*, 1995). In Jabalpur also a high degree of chloroquine resistance was recorded by Subbarao *et al* (1992).

Thus arteether which shows rapid schizontocidal action and brings about quick clinical improvement (Khapra, 1997) with low recrudescence rate will be of great use in areas of high drug resistance. The suggestive gametocytocidal action (Mohapatra *et al*, 1996) of the drug will be an added advantage in cutting down the transmission of Pf malaria.

Table 1

Effect of α–β arteether on *Plasmodium falciparum*. Fever and parasites clearance time in patients of different geographical area of central India.

District	Sex		Mean age	MFCT (hours)	MPCT (hours)	Parasitemia/mm³ (Mean ± SD)							
	M	F				D0	D1	D2	D3	D7	D14	D21	D28
Jabalpur	18	12	32.47 ± 12.98	37.60 ± 18.51	29.60 ± 10.32	5,453.27 ± 9,848.97	1,914.17 ± 2,113.39	0	0	0	0	904	0
Mandla	3	13	30.00 ± 12.54	32.06 ± 18.20	33.00 ± 12.00	11,343.50 ± 18,034.64	1,922.67 ± 3,499.26	0	0	0	0	0	22,282

MFCT - Mean fever clearence time
MPCT - Mean parasite clearence time

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