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New Antimalarial Drug Development in India: Arteether α/β -a Blood Schizontocide

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In view of the expanding foci of chloroquine and multiple drug resistant *Plasmodium falciparum* and increasing incidence of seizures due to cerebral malaria, there has been an urgent need for developing fast-acting blood schizontocides, for the control of the complicated malaria infections. Considerable work had been going on in China and other South - East Asian countries and US on the blood schizontocidal activity of artemisinin (qin-ghaosu) and its derivatives such as artemether and artesunate but their utility has been limited due to high recrudescence rate among *P. falciparum* cases treated with these drugs.

The present communication reports the development of α/β-arteether (30:70 mixture of enantiomers) as a fast-acting blood schizontocide. This compound exerts curative blood schizontocidal action against *P. berghei* (sensitive strain), *P. yoelii nigeriensis* (chloroquine, quinine and mefloquine resistant line), *P. knowlesi* (resistant to mefloquine) and *P. cynomolgi* B (sensitive strain). In addition, arteether has shown no adverse pharmacological effect in animal models, is safe in subacute toxicity, and has no teratogenic effect in rats and rabbits. Phase I clinical trials (safety/tolerance studies) with arteether in healthy subjects had been completed.

The drug arteether (α/β) has also completed multicentric clinical trials in *P. falciparum* endemic areas and was found to be effective and marketed in 1997 as E. Mal. This drug is specifically useful in the control of drug-resistant malaria and as a potential compound for the treatment of severe complicated malaria including cerebral malaria. Arteether has higher safety margin compared to other artemisinin derivatives, has longer half-life, and produces high cure rates when administered in a short 3- dose (intramuscular) regimen.

Key Words: Malaria, Cerebral malaria, Plasmodium, α/β arteether, Arteether β, Blood Schizontocide, Gametocytocide, Antimalarials, E.mal drug-resistance, Artemisnin derivatives

Introduction

Recent reports of the WHO Programme for the Control of Tropical Diseases (WHO, 1997, 1999) point out that the global malaria situation continues to be serious in tropical countries due to complications of severe *Plasmodium falciparum* malaria. Mortality of children under-five years of age takes a toll of one million cases in Africa South of Sahara alone. The emergence and fast spread of chloroquine-resistant as well as multi-drug resistant strains of *P. falciparum* are posing a serious threat to global efforts to control malaria. *P. vivax* strains showing resistance to chloroquine have also started emerging (Collignon 1991, Whitby et al. 1989). The present situation of malaria is :

- 2020 million human beings at risk of contacting disease.
- 300-500 million people suffer from malaria annually.
- 1.5-2.7 million deaths occur due to malaria annually, out of which 19500 deaths due to malaria have been recorded in India (Sharma 1998). NAMP (2003) has recorded only 1770 deaths due to malaria during 2001-2002 in the country. MOH (2000-2001) reported 3452 deaths during 1997-2000.
- Drug and insecticide resistance is increasing and it is doubtful that vector control can be achieved.

Chloroquine resistance of *P. falciparum* was first documented in 1960, amodiaquine in 1961,

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proguanil, pyrimethamine and mepacrine in 1963, quinine in 1964, quinine+ tetracycline in 1974, mefloquine, Metakelfin and Fansidar in 1981, pyronaridine in 1982 and Fansimef in 1985, while chloroquine resistance of *P. vivax* was first reported in 1989. The areas of *P. falciparum* resistance to chloroquine, Fansidar, quinine and mefloquine are gradually expanding (Bunnag et al. 1986, 1995, Karbwang et al. 1992, 1995, Looareesuwan 1994, Karbwang & Harinasuta 1992, Boudreau et al. 1982, Harinasuta et al. 1990.

- The level of resistance to most of the conventional anti-malarials is on the rise in South-East Asia, Africa and Southern America.
- Resistance to chloroquine in India is fast spreading in most of the states and the response of nearly 30% *P. falciparum* cases to chloroquine is gradually decreasing according to WHO estimates (Sharma 1998). According to latest NAMP (2003) report high level of chloroquine resistance (R-II and R-III) has spread to 29 states (251 PHCs), while sulphapyrimethamine resistance has been encountered in seven Indian states (12 PHCs).
- During 1998 there were 2.10 million malaria cases in India compared to 2.66 million in 1997 (National Anti-malaria programme reports by Shiv Lal et al. 1998 and Shiv Lal 1999). During 2000 and 2001 the number of malaria cases have been reported to be 2.03 and 2.09 millions respectively, out of which 50% cases are of *P. falciparum* (NAMP Report 2003).
- National Anti-Malaria Programme (NAMP) in India consumes nearly 30% of the Union Health Budget of Govt. of India (Shiv Lal et al. 1998). During VIII Five year plan (1992-93 to 1996-97), NAMP has spent Rs. 604.80 crores for malaria control. An anticipated expenditure of Rs. 21,500 lakhs annually will continue for malaria control operations in the country (NAMP 2003).
- There is already multi-drug resistant malaria in Thailand and new drugs are needed to combat drug resistant malaria.
- Medicine for Malaria Venture (MMV) aims to develop one new drug every 5 years (WHO 1999).

Historical Studies on Artemisinin Derivatives

The potential antimalarial value of *Artemisia annua* L., a Chinese herb, was first documented in Zhou Hou Bei Ji Fang (Handbook of Prescriptions for Emergency Treatments) written as early as 340 AD by Ge Hong of the Eastern Jin Dynasty. Qinghao preparations made from this plant have been used extensively in the Chinese traditional medicine for the control of malaria (Anon. 1979). The active antimalarial constituent of this plant isolated in 1971 was described as a new type of sesquiterpene lactone with a peroxy group and designated as artemisinin (Qinghaosu) (Anon. 1979). Its antimalarial activity against experimental rodent malaria infection was first observed in 1971 (Anon. 1982a). Since then, numerous investigators have studied the blood schizontocidal activity of artemisinin and its oil-soluble derivative β-arteether (Dutta et. al 1987, Anon. 1982b). Because of the high recrudescence rate of drug-resistant falciparum cases treated with artemisinin, efforts have been continued to develop more active oil or water soluble derivatives, such as α-arteether, αβ-arteether, β-arteether, artemether, sodium α- & β -artelinate, artesunate and artesunic acid (Dutta et al. 1998, Lin et al. 1987, Kamboj & Dutta 1998, Valecha & Tripathi 1997). In order to improve the cure rates obtained with artemether and artesunate alone, their combinations with mefloquine are being strongly advocated to tackle the problem of multi-drug resistant *P. falciparum* (see Kamboj & Dutta 1998). Progress on artemisinin research upto 1993 had been reviewed by Welcome Trust group (Anonymous, 1994).

The Chinese workers had reported the activity of β-arteether, with SD_{90} value of 1.95 mg/kg against chloroquine resistant *P. berghei*, while the activity of α-arteether, had not been investigated by them.

The World Health Organization had accorded high priority to the development of fast-acting artemisinin derivatives as blood schizontocides for the emergency treatment of cerebral malaria as well as for the control of multiple drug resistant *Plasmodium falciparum* (WHO 1985). Initial reports on clinical trails in severe malaria cases in China with artemisinin and its two derivatives, namely, sodium artesunate and artemether, were very encouraging. The cure rate obtained in cerebral malaria cases being 92.6% with artemisinin, 96.7% with sodium artesunate and 94.1% with artemether (Anon. 1982c). These three compounds were also evaluated among the chloroquine-resistant *P. falciparum* cases, and cure rates of 39.5%, 47.6% and 94.2% respectively were reported (Anon 1982c). Although clinical trails with artemether were continuing in China and elsewhere, the

World Health Organization had given preference to development of β-arteether, for the treatment of both cerebral malaria and multiple drug–resistant malaria cases, since artemether is likely to produce methanol toxicity (Brossi et al. 1988, WHO 1985, 1987).

Arteether is the ethyl ether derivative of dihydroartemisinin which is a sodium borohydride reduction product of artemisinin. The objective of the WHO CHEMAL's programme encouraged the development of arteether as a single dose parenteral treatment for severe and complicated *P. falciparum* infection. The choice to develop β-arteether, rather than artemether was based on the fact that arteether would be more lipophilic and its metabolic breakdown gives ethanol and not methanol, which would avoid the problems of methanol toxicity that can arise from the metabolic formation of formaldehyde and formic acid (Brossi et al. 1988, Ritchie 1985). Arteether because of its high solubility in oil and more lipophilic nature, would also be able to readily cross the blood-brain barrier and effectively control the cerebral malaria which is primarily caused by blockade of cerebral microcapillaries by the parasites. In view of the expanding foci of chloroquine and multiple drug resistant strains of *P. falciparum* and increasing seizures due to cerebral malaria, there has been an urgent need for developing fast-acting blood schizontocides, for the control of these complicated malaria infections.

Development of α/β-arteether

Since 1986, efforts were therefore, directed to develop jointly by CDRI-CIMAP, Lucknow, α/β-arteether, (a 30:70 mixture of enantiomers) as a fast-acting blood schizontocide specifically for the control of drug-resistant malaria and as a potential compound for the control of cerebral malaria cases. α/β-arteether, was patented jointly by CIMAP-CDRI in 1990 (Vishwakarma R A, Thakur R S, Dutta G P and Bajpai R -Indian Patent No. 173947/1070 DEL 90) as a novel blood schizontocide. The major antimalarial activities of α/β-arteether, and clinical profile of the drug have been briefly reviewed by Dutta et al. (1994), Dutta and Tripathi (1996), Asthana et al. (1994, 1997), Dutta et al. (1998), Kamboj and Dutta (1998) and Jain et al. (2000).

Antimalarial Studies

Blood Schizontocidal Activity of α/β-arteether

α/β-Arteether, has shown fast-acting blood schizontocidal action against the following experimental malaria models:

P. berghei (sensitive strain): Curative dose is 5 mg/kg x 3 doses (Dutta et al. 1987, Bajpai et al. 1988)

P. yoelii nigeriensis (lethal multi-resistant strain) showing complete resistance to chloroquine, mefloquine and quinine (Dutta & Pandey 1986). Curative dose is 5mg/kg x 3 doses in Swiss mice (Dutta et al. 1989b).

P. knowlesi- a cerebral malaria model: Curative dose is 12 mg/kg x 5 doses (Bajpai et al. 1989b).

P. cynomolgi B – a *P. vivax* like model : Curative dose of α/β-Arteether, is 5mg/kg x 3 doses (Dutta et al. 1989a, Tripathi et al. 1991).

P. fragile –a cerebral malaria model: Curative dose of α/β-Arteether is 10mg/kg x 3 doses (Tripathi et al. 1996).

Gametocytocidal Activity

P. cynomolgi B - *Anopheles stephensi*- Rhesus model: α/β Arteether shows high gametocytocidal activity at 10 mg/kg dose (Tripathi et al. 1990, 1996).

Casual Prophylactic and Antirelapse Activity

Arteether has no casual prophylactic or antirelapse activity (Bajpai et al. 1989b).

Pharmacological Studies

α/β-Arteether had been found to be devoid of any significant pharmacological effect on CNS, CVS or urinary system. No drug related adverse pharmacological effect was reported (Kar et al. 1989). LD50 of drug is 1267.33 mg/kg in Swiss mice. (i.m.) and it is safest among the artemisinin derivatives (Dutta & Tripathi 1996).

Sub-acute Toxicity Studies

Systemic toxicity studies on arteether were undertaken by Sethi et al. (1988) in two hosts, namely rats and monkeys. Experimental groups of rats were injected with arteether at 3 dose-levels (low, high and toxic), i.e. 2.5, 5.0 and 10.0 mg/kg body weight x3 consecutive days per week for a period of 4 weeks. The monkeys were given 7.5, 15.0 and 30 mg/kg doses for 3 consecutive days per week for a period of 4 weeks. Detailed subacute toxicity tests on arteether treated rats and monkeys showed no significant change in body weight, haematological, bio-chemical, histopathological parameters of the test animals. Arteether has been found to be safe in regulatory subacute 1 month toxicity studies and the compound was

recommended for clinical trials in humans (Sethi et al. 1988).

Teratogenicity Studies

Teratogenicity studies in rats and rabbits showed that α/β-Arteether, has no teratogenic potential and is a safe drug (Sinha & Sethi 1994).

Clinical Trials with α/β Arteether

On the basis of Dossier (1988) on arteether α/β-submitted to the Drugs controller Govt. of India, permission was granted to conduct clinical trials at CDRI.

Phase-I : Single Dose Tolerance Study

Phase I single dose tolerance study with α/β arteether (30:70) was undertaken at the Central Drug Research Institute, Lucknow. Thirty healthy human volunteers who consented to undergo the trial as per approved protocol completed the study. The trial was double blind placebo controlled and non-crossover. The dose of arteether injection ranged from 20 to 300 mg; 6 volunteers received placebo injection, while 4 each were given 20, 50, 100, 150, 200 and 300 mg arteether in a gradually escalated manner (Asthana et al. 1994).

In all cases, single injection of arteether/placebo (oil) was tolerated well and no tenderness, swelling or discomfort was experienced at the site of injection. Recording of clinical parameters and detailed haematological and biochemical investigations, ECG and urinalysis did not reveal any abnormality (Asthana et al. 1994).

Phase I: Multiple Dose Tolerance Study

After establishing the safety of single doses of arteether ranging from 20 to 300 mg in healthy human volunteers, multiple dose tolerance study was undertaken at CDRI Clinical Pharmacology Unit, Seth G.S. Medical College, Mumbai. Twenty healthy human volunteers who executed written informed consent completed the study as per approved protocol. Initially, the first group of 10 volunteers was given arteether (100mg) injection (intramuscular) once a day on three consecutive days. Subsequently, the second group of 10 healthy human subjects was treated with 150 mg of arteether by intramuscular injection on 3 consecutive days. All the 20 volunteers who completed multiple dose tolerance study were males. Each volunteer was subjected to a detailed history-taking, clinical examination and laboratory investigations before the administration of the first dose of arteether injection with the aim of having initial baseline pretherapy values of each parameter. No untoward reaction, experiences or drug-induced abnormalities could be detected in clinical and laboratory parameters and the variation observed in organ function tests was within normal limits, except a transient rise in transaminase levels (SGOT/SGPT). Thus, it can be concluded that arteether therapy with 100 and 150 mg doses given as intramuscular injections once a day on 3 consecutive days, are well tolerated and safe (Asthana et al. 1994).

Phase II and III Clinical Trials with α/β Arteether

The clinical data on phase II/III multicentric studies on arteether carried out against uncomplicated/complicated severe *P. falciparum* infections has been partly published by clinical groups (table 1). In a preliminary study on the clinical efficacy of arteether in patients with uncomplicated *P. falciparum* infections, a dose of 150 mg daily x 3 days (im), was reported to produce a cure rate of 85% (Asthana et al. 1996). The detailed report on first clinical trail (Phase-II) with α/β-Arteether among 51 uncomplicated *P. falciparum* cases has been published by Mishra el al. (1995). The dose of 150 mg daily for 3 consecutive days by im injection, has shown very high curative activity in field trials. Complete parasite clearance was noted in 43% cases at 24 hr, in 80% cases at 48 hr and in 98% cases at 72 hr. Fever clearance time was 52.04 hr ± 27.09. Drug was well-tolerated, and 86% cure rate was recorded.

Thirty uncomplicated *falciparum* malaria cases completed phase III clinical trails of the drug α/β-Arteether in a malaria endemic tea garden of district Dibrugarh, Assam. Arteether was given intramuscularly in once a day dose of 150 mg for three consecutive days. The cure rate was 100 percent with mean fever and parasite clearance time of 42.4±17.5 and 37.6±13.6 hr, respectively. Recrudescence/reinfection rate was 6.7 percent (Mohapatra et al. 1996). Mohanty et al. (1997) have also reported the efficacy of the drug in severe falciparum malaria. Fifty patients with severe falciparum malaria were given intramuscular arteether, 150 mg, once daily on 3 consecutive days. The median fever clearance time was 72 hr (range 12-120 hr) and the median parasite clearance time was 2 d (range 1-4 day). Rapid recovery from coma was observed in cerebral malaria cases after a median of 18 h (range 6-72 hour). Two patients died and both

Table 1. *Summary of the clinical trials data of P. falciparum cases treated with arteether α/β (150mg/day x3 dose)*

Reference	Mishra et al. (1995) & Asthana et al. (1996)	Mohapatra et al. (1996)	Valecha et al. (1997)	Mohanty et al. (1997)	Singh et al. (1998)
Clinical Trials	Phase-II	Phase-III	Phase-III	Phase-III	Phase III
No. of cases	51 uncomplicated	30 uncomplicated	50 uncomplicated	50 (33 cerebral malaria) severe Pf	46 Uncomplicated
Mean parasitaema	0.6% (0.05-14.5)	-	0.65%	-	-
Mean body temperature	38.7±1.05°C	99-106°F	38.21±1.02°C	-	-
Mean PCT	48 hr (24-96)	37.6 ± 13.6	19.94±6.87	48 (24-96)	30.78± 10.92 hr
Mean FCT	52.04(±27.09)	42.4±17.5	37.81±21.67	72(12-120)	
Recrudescence rate/reinfection	14%	6.7%	6%	(7 patients) 20%	6.7%
Cure rate	86%	100%	94%	80%, recovery from coma 18 hr range (6-72).	93.3%
Gametocytocidal activity	-	Present	-	-	Present

had cerebral malaria and haemolytic jaundice. Recrudescence within 28 days was observed in 7 patients.

Another phase-III clinical trial was conducted by Valecha et al. (1997) in 50 acute uncomplicated falciparum malaria cases from MRC, Delhi. Their mean parasitaemia on day 0 was 0.65%. A standard dose of 150 mg i/m for three consecutive days resulted in mean parasite and fever clearance times of 19.94±6.87 and 37.81± 21.67 hours respectively. Within 48h, 70% of the cases became afebrile and the peripheral blood smear was negative in 100% of the cases. The drug was well-tolerated. Three cases (6%) had recrudescence within 28 days. It was concluded that α/β-Arteether is a safe effective and rapidly acting blood schizontocide. Post-marketing surveillance of arteether for the control and management of uncomplicated, severe complicated and cerebral malaria cases was carried out to monitor drug response. Arteether α/β has been cleared by Drugs controller Govt. of India, for hospital use in severe malaria cases. The drug is not so far approved for treatment of malaria in pregnant women due to its possible teratogenic action. Clinical trials to obtain permission for use of arteether in paediatric group are in progress (O.P. Asthana-unpublished data). Singh et al. 1998 reported a cure rate of 93.3% among 46 uncomplicated cases treated from Jabalpur and Mandla (table 1).

The results of pooled data of Phase-III multicentric clinical trials with α/β arteether (150 mg imx3 doses) have been summarized by Dev et al. (1998) and Asthana et al. (2001a, b). Dev et al. (1998) had summarized the clinical trial (Phase-III) data from Assam based on 41 febrile malaria patients having moderate to acute *P. falciparum* parasitaemia (26 cases were categorized as uncomplicated and 14 cases as complicated *P. falciparum*). All these cases were treated with α/β arteether and 100% cure rate was reported in this study. The authors conclude that α/β arteether also showed gametocytocidal action in two cases while in third case the gametocyte count persisted though, the viability of persisting gametocytes was not tested. In another report, 267 patients of uncomplicated *P. falciparum* from different centres were treated with arteether and the cure rate recorded was 97% (Asthana et al. 2001a). The third report summarized results of 211 compli-cated *P. falciparum* cases from different clinical centres who were treated with arteether and overall cure rate was 93% and mortality ranged between 4-8.5% at different centres (Asthana et al. 2001b). Out of 211 cases treated the mortality was recorded in 14 cases, out of which 10 cases died prior to completing 3 dose therapy.

Phase IV Clinical Trials with α/β Arteether

The data on post marketing surveillance of α/β arteether (30:70) has also been recently published by Asthana et al. (2002). In this study, 300 *P. falciparum* cases from states of Bihar, Gujarat, Madhya Pradesh, Maharasthra, Rajasthan and

Uttar Pradesh, who were admitted to hospitals, nursing homes/clinics, were treated with 150 mg arteether injection (im) daily for three consecutive days, and the results showed a cure rate of 98%. This study on arteether further confirmed its safety and very high efficacy of the drug. According to a recent report 1.8 million malaria patients had been treated with α/β arteether till June 2002 (Ramachandran 2002)

The major advantage of α/β arteether injection over β arteether, artemether or artesunate would be short 3 dose injection schedule with high efficacy aganist multidrug resistant *P. falciparum/ P. vivax* infections etc. Since arteether monotherapy is very effective by itself, its combinations with mefloquine or sulpha-pyrimethamine synergistic combinations would be planned to further potentiate its curative effects and reduce malaria mortality.

β Arteether Status

β arteether (Artemotil) injectible im formulation in sesame oil (vehicle) developed through the collaborative efforts between WHO/TDR, WRAIR and the Dutch company Artecef BV, had been approved on 22 May 2000 by Dutch registration authority for severe *P. falciparum* treatment (TDR News No. 63, Oct. 2000, p.-13). β Arteether (Artemotil) 150 and 50 mg injections in sesame oil are proposed for hospital use for 3 day treatment of severe *P. falciparum* cases among children and adults. Cumulative dose of 11.2 mg/ kg (approximately 672 mg total in 3 days) is recommended. Majority of drug β arteether is claimed to be metabolised to antimalarial metabolite dihydroartemisinin (Artenimol). However TDR News No. 63 Oct 2000 p.13 figure 2, does not show any significant plasma level of artenimol during 120 hr of treatment. It is surprising that β arteether injection (as sesame oil formulation) actually used for phase-II and III clinical trials was a longer 5-day dose schedule (3.2 mg/kg) on 1st day, followed by 1.6 mg/kg daily from day 2 to 5; total dose approximately 576 mg per 60 kg). Clinical trial data based on 5 day b arteether (in sesame oil formulation) showed lower cure rates (81-89%) among uncomplicated *P. falciparum* cases (Looareesuwan et al. 2002). With 5-day β arteether regimen the cure rate among cerebral malaria patients ranged between 73.2-79% (Moyou-Somo et al. 2001, Thuma et al. 2000). Although no drug related toxicity/neurotoxicity was observed in patients, the safety of sesame oil formulation of β arteether is still debated and is a matter of serious concern (Li et al. 2002).

Pharmacokinetics Studies

The pharmacokinetic data on artemisinin derivatives summarized below show that arteether has obvious advantages over other derivatives.

A pharmacokinetic study on β-Arteether had been carried out in dogs after the i.m. administration of a 25 mg/kg dose of arteether dissolved in sterile sesame oil and benzyl alcohol (vehicle). Benakis et al. (1991) clearly established that β-Arteether had an elimination half-life ($T_{1/2}$ b) of 27.95 ± 11.93 hr, which is considerably longer than that of dihydroartemisinin (2 hr), artesunate (45 min), artemether (6.5 hr) and artemisinin (1.6 hr). White (1994) had also reported that in human subjects, the elimination half-life of artemether was 11.1 - 13.2 hr after 10 mg/kg dose, artemisinin (oral or suppository) has 4.0-4.5 hr at the same dose, artesunate (i.v.) has 0.5-1.4 hr at 2.0-4.4 mg/kg dose and a half-life for arteether at 3.6 mg/kg dose was reported to be longest (23.1 hr). In single and multiple dose studies with β-Arteether, the elimination half-life of the drug has been reported by Kager et al. (1994) to be 23.1 hr after a single 3.6 mg/kg dose, and after a multiple 5 dose schedule, the half-life was found to be 69.30 hr. Kager et al. (1994) finally concluded that β-Arteether may have the longest half-life of all the artemisinin derivatives studied so far.

The clinical trial carried out by this Institute involving 51 *P. falciparum* cases treated with 3 doses (150 mg each) of α/β arteether (Mishra et al. 1995) showed extended parasiticidal action of drug up to 96 hr (i. e., 48 hr beyond the last arteether injection), which may be related to its long half-life. Morever, a 3 dose schedule of α/β arteether gave a parasitaemia clearance rate similar to that obtained by a 5-6 dose artemether or artesunate schedule which can be explained on the basis of the longer half-life of arteether (more than 24 hr) in comparison to other derivatives such as artemether (11.1-13.2 hr), artesunate(0.5-1.4 hr) and dihydroartemisinin (2 hr). Major metabolite of arteether, artemether, artesunic acid artesunate *in vivo* is dihydroartemisinin (DHA) which is responsible for antimalarial activity of these derivatives (de Vries & Dien 1996, WHO 2000).

Comparison of Arteether with other Artemisinin Derivatives

The toxicity of arteether had been studied by several workers. At this Institute, 7.5-30 mg/kg dose of α/β arteether (3 injections per week for 4 weeks) given to the rhesus monkey and 2.5-10 mg/kg doses given to rats were declared safe in regulatory toxicity trials (Sethi et al. 1988), which justified human clinical trials with arteether. Subsequent single dose and multiple dose phase I safety/tolerance clinical studies in human volunteers also had established the clinical safety of 100 and 150 mg doses given as i.m. injection once a day on 3 consecutive days in 20 volunteers and no undesirable side-effects related to the drug or oil vehicle were observed (Asthana et al. 1994).

Long-term toxicity studies on β-Arteether by Davidson (1994) in rats given 3 mg/kg/day dose for 28 days was reported to be safe. Brewer et al. (1994) also reported that 5-10 mg/kg dose of β-Arteether given for 28 days to rats and dogs was safe and without any neurological effects. Recent neurotoxocological studies with arteether in rhesus monkeys (Petras et al. 1997) and with artemether and artesunate in MDR *P. falciparum* cases further confirmed the clinical safety of these drugs when used at moderate recommended doses. Looareesuwan et al. (1997) also reported no evidence of neurotoxicity in earlier clinical trials of aresunate and artemether involving more than 2500 patients treated in Bangkok hospital for tropical diseases. In more recent study by Van Vugt et al. 2000 and WHO (2000), to-date no evidence of any neurotoxicity in humans has been found. Since the LD_{50} of arteether is 1267.33 mg/kg in mice (Dutta & Tripathi 1996), the drug has a higher safety margin than artemether and artsunate with LD_{50} doses of 263 and 475 mg/kg (i.m.), respectively (Anon 1982a).

WHO (1994) report had given high priority for completion of preclinical/toxicological/clinical evaluation of β-Arteether and artemether as potential antimalarials to be developed as life-saving drugs. β-Arteether (i.m.) has been recently registered by WHO for clinical use in endemic areas. However, the safety of artemether is still debatable. According to Brossi et al. (1988), β-Arteether would be relatively safer compared to artemether because the latter can produce methanol after cleavage in biological system which could generate methanol toxicity. Compared to arteether (LD_{50} 1267.33 mg/kg), the artemether is 4-5 times more toxic due to its lower LD_{50} (263 mg/kg) dose in mice. Clinically accepted treatment schedule for artemether is 600 mg in 5 days, while arteether can be given as 450 mg total human dose in a 3 day schedule to get the comparable or even better cure rate. Moreover, the arteether is more lipophilic and would have the possible advantage of its greater accumulation in brain tissue (Brossi et al. 1988). Our antimalarial studies against *P. cynomolgi* B clearly show that both β-Arteether and α/β-Arteether are equally curative (at 5 mg/kg x 3 doses), nevertheless we have preferred to develop α/β-Arteether (30:70 mixture) because of its ability to cure multi-resistant *P. yoelii nigeriensis* infection, ability to cure *P. knowlesi* infection – a cerebral malaria model, *P. fragile* infection – a model comparable to *P. falciparum*, and because of its gametocytocidal potential which can be exploited to interrupt malaria transmission. The drug has also successfully cleared regulatory animal pharmacology and sub-acute toxicity protocols acceptable by Drugs Controller General, India. The drug α/β-Arteether has been found safe in clinical trials and has given consistent high cure rate in multicentric clinical efficacy trials carried out in different parts of the country.

The Central Drug Research Institute and Central Institute of Medicinal & Aromatic Plants, Lucknow were jointly awarded CSIR Technology shield for developing α/β-Arteether as a new antimalarial drug (1998), and Govt. of India, Ministry of Science and Technology also gave National Technology award (1999) to CDRI/CIMAP jointly for developing arteether technology. Arteether α/β was marketed in 1997 as E-Mal. E-Mal (α/β-Arteether, 30:70)- drug for treating cerebral malaria has received Jai Vigyan Recognition from Govt. of India, Ministry of Science & Technology (on 19 Nov. 2002). E-Mal has been Internationally marketed to nearly 50 countries according to CSIR report.

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