Drug Therapy

Artemisinine and its Derivatives

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Malaria is endemic in most parts of India. Every year almost 2 million cases are reported by the National Malaria Eradication Programme. Globally 1-2 million children below the age of 5 years die annually due to malaria, 90% in tropical Africa. The potentially lethal malarial parasite *P. falciparum,* is increasingly becoming resistant to commonly used antimalarials [1]. The resurgence of malaria, particularly of the multidrug resistant strains, has resulted in the search for newer antimalarial drugs. Since 1979 several different formulations of such drugs, including artemisinine have been evaluated in China and later marketed^). With the recent introduction of Artemisinine in India, it would be timely to briefly review its current status in the treatment of malaria in our setting.

Mechanism of Action

Artemisinine is derived from plant *Aretemisia annua* (Quinaho)(3). Artemisinine and its derivatives are concentrated in parasitized erythrocytes and are effective blood schizontocides against all types of malaria including chloroquin resistant *P. falciparum* species. The structure and activity relation suggest that endperoxide bridge is essential for antimalarial activity. Although the precise mechanism of parasiticidal effect remains uncertain, the drug is postulated to cause free radical damage to the parasite membrane system(4). They stop the parasite development in early stages and prevent subsequent rosetting and cytoadherance, both of which are important pathophysiological mechanisms in severe malaria.

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Pharmacokinetics

Artemisinine is rapidly absorbed from the gastrointestinal tract with a peak plasma level occurring at 1h and is hydrolyzed *in vivo* to active metabolite dihydro artemisinine. Following this, the parent compound and metabolite are widely distributed in the tissues and eliminated rapidly with half life of 4 h. In plasma, the peak plasma concentration of Artemether occurs in 6h and then declines with elimination of half life of 4-11 h. After administration of Artemisinine suppositories in a single dose of 10 mg/kg, the mean (SD) time to peak concentration is 11.3 (5.9) h and elimination half life is 4.1 (0.6) h.

Clinical Use

Table I summarizes data from clinical trials of this drug (2,5-11). Although most of the trials relate to adult subjects, sufficient data has accumulated in children documenting it's efficacy and safety in this age group too. The reported cure rates range from 52-98% depending on the duration of therapy. With 7 day therapy, the cure rate is higher (92 to 98%). Addition of another antimalarial, tetracycline or mefloquin also enhances the clinical response. There is a significant reduction in mortality in patients with *P. falciparum* malaria, treat-

TABLE I-*Summary of Clinical Studies*

Reference	Place [year]	Sample size Age group	Type of malaria trial	Nature of	Success rate	Conclusion
2	China [1979]	2150 202 (641 children)	*P. Fakiparum* *P.vivax*	Randomized	98% after 7 d 85% after 5d 52% after 3d	Recrudescence rate was higher after 3d than 7d therapy
5	Oxford (1991)	Each group 28 Adults	*P. fakiparum*	Randomized comparison	Not calculated	It is equally effective IV and IM
6	Brazil (1992)	Each group 88 Adults	*P. fakiparum*	Triple blind random controlled	*77%*	Effective in combination with tetracycline
7	Thailand [1991]	Each group 50 Adults	*P. fakiparum*	Double blind randomized	72%	Duration of treatment determines efficacy
8,9	Thailand [1991]	1000	*P. fakiparum*	Randomized comparative	92.50%	With Mefloquin it acc-elarates clinical response
10	Vietnam (1995)	Not specified	*P. fakiparum*	Randomized comparative	92.5% artesunate 80% quinine	Significantly reduces mortality
11	Gambia (1996)	576 Children	*P. fakiparum* Cerebral malaria	Open randomized	79.5% artemether 78.5% quinine	As effective as quinine in treatment of cerebral malaria

ed by artesunate. It is as effective as quinine for treatment of cerebral malaria.

Doses and Modes of Administration

The recommended doses and regimen of administration are summarized in Table II. Parenteral preparations are useful in severe and complicated malaria, where the patient is comatose or vomiting. Artemisinine suppositories represent a major advance in treatment of severe malaria in rural areas where injection cannot be given. The currently available preparations in India are summarized in Table III.

Adverse Drug Reactions

The drug and its derivatives have proved to be fairly safe. Only a few adverse effects are reported in man. Transient heart block was noted in 1/82 patients with artesunate and 3/39 cases with arte-mether (l). After oral artesunates, the minor side effects reported include fever (25%), tenesumus (6%), abdominal pain (3%) and diarrhea (1%). In animal studies the incidence of abortion was more in the first trimester(12). However, the safety in pregnancy in humans is not as yet established.

TABLE III—Recommended Doses and Regimens of Administration.

Drug	Dose (mg/kg)	Therapy time
Oral		
Artemisinine	25	Id
	12.5	2&3d
Artesunate*	5	Id
	2.5	2 & 3 d
Artesunate	5	5 d
Artemisinine	10	5 d
Parenteral		
Artesunate	1.5	1 d-twice
		5-7 d-once
Artemether	3.2	1 d
	1.6	Until oral therapy

Can be given with Mefloquin 15 mg/Kg.

TABLE II- Artesunate Preparations available in India.

Preparation	Cost	Name	Company
Tablet (50 mg)	4tab Rs. 60/-	Falcigo	Cadila
	4tab Rs. 60/-	Arnate	Mescos Pharma
Injection (60mg/ml)	Rs. 111/-	Falcigo	Cadila

Recommendations

On the basis of available evidence, the following recommendations have been made for the use of this drug(12). Artemisinine and its derivatives are effective alternate antimalarials for various multi drug resistant strains of P. falciparum and P. vivax. Artemisinine, Artesunate and Artemether should be used in the treatment of resistant malaria where Quinine and Mefloquin have proved ineffective. To prevent their haphazard use they should not be prescribed by a general practitioner. They should be prescribed after microscopic examination of blood, confirming the diagnosis of P. falciparum malaria which is resistant to initial multi-drug therapy. The drug should be used for a minimum period of 3 days and in combination with an effective dose of mefloquin or any other long acting effective drug in order to achieve > 90% cure rate.

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