ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 1 (3) 2013, 66-69

REVIEW ARTICLE

ARTEROLANE MALEATE AND PIPERAQUINE PHOSPHATE: A NEW OPTION IN THE TREATMENT OF *PLASMODIUM FALCIPARUM* MALARIA

*[1]Suruchi Aditya, [1]Ruchika Nandha, [1]Kavita Sekhri , [2]Prof. Satyanand Tyagi

[1]Deptt. Of Pharmacology,Dr Harvansh Singh Judge Institute of Dental Sciences, Sector 25,Chandigarh, India-160 014

[2]President, Tyagi Pharmacy Association & Scientific Writer (Pharmacy), Chattarpur, New Delhi, India-110074

ABSTRACT

Malaria is holoendemic in India, claiming thousands of deaths annually. Recent data suggests that the burden of malaria, the most significant parasitic disease in the world, is increasing. India's expansive geography and diverse climate supports ideal environment for sustaining malarial parasites and their vectors. The National Drug Policy of India recommends artemisinin based combination treatment for the management of malaria. Although the use of Artemisinin has strengthened global efforts to combat malaria, multi-drug resistance has increasingly become a major impediment to malaria control. The complete clearance of parasites is dependent on the partner drug in the combination being effective and also persisting at parasiticidal concentrations until most of the infecting parasites have been killed. Arterolane maleate (150mg) and piperaquine phosphate (750mg) combination is a novel antimalarial combination that is not based on artemisinin. This combination provides rapid clearance of parasitemia and malaria-related symptoms, coupled with prevention of recrudescence. Additionally, a short course treatment of 3 days encourages compliance. Combination of arterolane and piperaquine is a safe and well-tolerated drug combination, making it a welcome addition to the armamentarium against *Plasmodium falciparum*.

KEYWORDS: malaria, *Plasmodium falciparum*, arterolane, piperaquine

INTRODUCTION:

Malaria is a major public health problem infecting 300-500 million people worldwide and causing more than one million deaths annually globally. An endemic protozoal disease in India with an estimated 70-100 million cases each year, *Plasmodium falciparum* is responsible for half of these cases. [1]

Acute Parasite Index (API), an indicator of the disease incidence is reportedly less than 2 in most parts of India. However, endemic regions with API more than 5 are spread in the states of Rajasthan, Gujarat, Karnataka, Goa, southern Madhya Pradesh, Chhattisgarh, Jharkhand, Orissa and the North–Eastern states.[2] Recent history shows that *Plasmodium falciparum* incidence in India has increased from 13% in 1978 to over 50% in 2009. Lack of accurate estimates for population at risk is one of the elementary problems in defining intervention strategies against malaria. Many studies argue that malaria incidence is between 9 and 50 times greater than reported. [3, 4, 5]

Efficacy studies of antimalarial drugs done in India since 1978 show that resistance of *Plasmodium falciparum* to chloroquine is present across all regions of the country. World health organization (WHO) recommends the use of Artemisinin based Combination Therapy (ACT). It involves the use of two or more blood schizonticidal drugs with independent modes of action and thus unrelated biochemical targets that are combined for parasiticidal effect.

As recommended by WHO, the National Drug Policy in India uses artesunate plus sulfadoxine-pyrimethamine (AS+SP) as first line treatment for *Plasmodium falciparum* infection. Treatment of *Plasmodium falciparum* malaria depends on the severity of infection, status of the host and drug sensitivity pattern in the locality. Local antimalarial drug resistance patterns, government treatment guidelines, tolerability, availability and gametocidal activity guide the selection of the appropriate therapeutic agent. [5] It is important to monitor the in vitro drug susceptibility of *Plasmodium falciparum* regularly to guide the national drug policy. Many collaborative centers, agencies and projects are working towards the goal of enhancing malaria intervention and control programs in India.

THE SUCCESS OF ACT AND THE FUTURE:

Artemisinin and its derivatives produce rapid clearance of parasitaemia and rapid resolution of symptoms. They reduce parasite numbers by a factor of approximately 10,000 in each asexual cycle, which is more than any current antimalarial.

Artemisinins are highly efficacious, rapidly active with action against a broad range of parasite developmental stages. They reduce gametocytogenesis by

*Corresponding author: Dr. Suruchi Aditya | Email: suruchiaditya@rediffmail.com

8-18 folds. This decreases the likelihood that gametocytes carrying resistance genes are passed onwards and may reduce malaria transmission rates. [6]

The success of ACT has been reflected in reduced API over the recent years. The major threat today is the potential for resistance to arise in *Plasmodium falciparum* against artesunate or its partner drug. Interventions aimed at preventing drug resistance generally focus on reducing overall drug pressure through more selective and restrictive use of drug, improved prescribing and follow up practices, improved patient compliance and use of drug combinations. Restrictive drug use also implies improving the diagnosis of malaria.

THE PROBLEM OF DRUG RESISTANCE:

Antimalarial drug resistance has been defined as "ability of a parasite strain to survive and /or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject." This definition was modified to specify that drug in question must gain access to the parasite or the infected red blood cells (RBCs) for the duration of time necessary for its normal action. [6]

Conditions leading to malaria treatment failure contribute to development of resistance and include incorrect dosing, non-compliance with duration of dosing regimen, poor drug quality, drug interactions, poor or erratic absorption and misdiagnosis. Additionally, factors that decrease the effectiveness of immune system in clearing parasite residuum after treatment also increase survivorship and intensification of resistance. [6]Rate at which resistance develops in a given area depends on the intensity of transmission, initial prevalence of mutations, intensity of drug pressure, population movement between areas or its strains and so on. [6]The use of an alternative drug reduces drug pressure, which is thought to be the single most important factor in the development of resistance. The origin of drug-resistant parasite in India seems to be from South-East Asia (Cambodia-Thailand). [3,7]

Increased parasite population with higher number of mutations associated with antifolate resistance is also a serious concern as ACT in India has the SP component. [7] Concerns have risen regarding pre-existing resistance to sulfa-pyrimethamine which could compromise combination treatment. [1]Reduced efficacy of SP treatment was observed in some recent surveys in the north-east but molecular markers for SP resistance are well known so that surveillance is possible. [8] Singh *et al* reported a recent epidemic in central India, where ACT was being used. [9]

Recent studies focus on the evaluation of different forms of ACT, which may form an alternative to AS + SP combination. These back-up treatments include artemisinin derivatives (artesunate, artemether, artemotil, dihydroartemisinin), combined with mefloquine, amodiaquine, lumefantrine, piperaquine and pyronaridine. [10, 11] The choice of the combination partner, however, can be difficult. Mefloquine has been associated with an increased risk of neuropsychiatric effects and stillbirth. Clindamycin is safe, but both medicines (clindamycin and the artemisinin partner) must be given for 7 days. Primaquine and tetracyclines should not be used in pregnancy. Amodiaquine, chlorproguanil-dapsone, and halofantrine have not been evaluated sufficiently to permit positive recommendations.

Studies involving in vitro assessments of *Plasmodium falciparum* resistance have shown a high degree of resistance to chloroquine followed by monodesethylamodiaquine as well as absence of resistance to mefloquine and dihydroartesunate.[12] In a comparative efficacy study by Saha *et al*, PCR-corrected efficacies were AS+SP: 90.6%; amodiaquine-lumefantrine: 95.9% and artemisinin-mefloquine:100%. Failure rate of AS+SP (9.5%) was attributed to SP failure due to prevailing mutations in the genes *plasmodium falciparum dihydrofolate reductase (pfdhfr) and plasmodium falciparum dihydro pteroate synthase (pfdhps).* [13]

PROBLEMS WITH ACT:

In order to make best use of Artemisinin based therapies, it is critical to address issues of delivery, access and cost. It is well known that continuous supply of new and affordable drugs along with implementable control measures will help reduce overall burden of the disease. Artemisinin is derived from plant sources, making it expensive. The crop of artemisinin depends on weather and other factors, harvest varies and prices change accordingly. There is potential for mismatch in demand and supply. Another concern is the extent to which components might be used unofficially and incorrectly for monotherapy outside official health services, promoting resistance.

These facts point towards a need to identify a new alternative, effective and affordable antimalarial regimen.

A NEW ANTIMALARIAL COMBINATION:

Fixed dose combination of arterolane maleate (150 mg) and piperaquine phosphate (750 mg) has been recently developed and approved by FDA as a once-a day therapy for three days for the treatment of acute, uncomplicated *Plasmodium falciparum* malaria.

Arterolane, a synthetic trioxolane, is a rapidly acting blood schizonticide against all blood stages without effect on liver stages. It undergoes reductive cleavage in the food vacuole by ferrous iron to generate free radicals which inhibit PfATP6, a sarcoplasmic endoplasmic reticulum calcium ATPase encoded by *Plasmodium falciparum*. The irreversible redox reaction between antimalarial peroxides and heme produces carbon-centred radicals or carbocations that alkylate heme and proteins, leading to perturbation of lipid components of the parasite digestive vacuole. [14]

Piperaquine is a bisquinoline that inhibits heme-digestion pathway in the parasite vacuole.

The combination has high plasma protein binding, extensive volume of distribution. Arterolane is metabolized by oxidation of adamantane moiety. CYP3A4 contributes to 30% of metabolism. Piperaquine is metabolized by mono and dioxygenation. Half-life of arterolane is 1-3 hour, while piperaquine has half-life of 17-23 days. The drug is independent of dietary restrictions for fatty foods or milk, as is the case with older antimalarial drugs. It has synthetic source-so supply can be maintained at low cost. The drug is to be taken as one tablet a day. Three-day course makes it a convenient option, leading to better compliance. [15, 16]

In a randomized double blind multi-center dose finding phase II trial conducted in 230 patients in Thailand, India and Tanzania, PC90(median time to 90% parasite clearance) was longer in arterolane maleate and piperaquine phosphate group receiving 50 mg (19.4h) dose compared with groups receiving 100mg (12.8h) and 200mg dose (12.6h) ($p<0.01$). The polymerase chain reaction (PCR)-corrected adequate clinical and parasitological responses on day 28 were 71% and 72% for 100 and 200mg dose. Recrudescence rates after PCR adjustment were observed to be between 28% and 37% in the study groups. [17]

In a recent randomized, multicentric, parallel group, open label clinical trial, no treatment failure was noted in the arterolane-piperaquine group, while one patient receiving artemether/lumefantrine combination failed treatment on day 28. There was no difference in the median parasite clearance time (30 hours in both groups) or median fever clearance time (24 hours in both groups) after administration of the 2 study treatments. [18]

ECONOMIC EFFECTS:

The economic effects include direct costs for treatment and prevention as well as indirect costs such as lost productivity from morbidity and mortality, time spent seeking treatment and diversion of household resources. [6] In one study, every rupee invested in malaria control produced a direct return of Rs. 19.70. The estimated man-days saved were 1,328.75 million per year. [19] In another recent study, artemisinin+mefloquine cost was evaluated to be $2.594 per course. Several commercially produced co-formulated ACTs are now available for less than $2 including artemether-lumefantrine and dihydroartemisinin-piperaquine. [20]In another study conducted in children, for dihydroartemisinin+piperaquine, the average cost per treatment success was US$ 2.95, with an 87% probability of the cost–effectiveness ratio being < US$ 50.00. For artemether+lumefantrine the average cost per treatment success was US$ 6.97, with a 99% probability of this being < US$ 50.00. The incremental cost–effectiveness ratio of artemether+lumefantrine relative to dihydroartemisinin +piperaquine, the next best alternative, was US$ 10.60 per success, with a 92% probability of this ratio being < US$ 50.00. For *P. vivax* , dihydroartemisinin +piperaquine was the most effective treatment, with an average cost saving of US$ 0.18 per success in a usual care setting and a > 99% probability of the cost per success being < $1.00.[21]

With ACTs currently costing around five to 10 times more than the traditional monotherapies, there needs to be a radical change in the approach to how they are funded and supplied in order to ensure that they are accessible and affordable to those who most need them. Moreover, unlike Artemisinin based treatments, arterolane and piperaquine combination has a synthetic source that would allow quick scale-up in production. The cost of a three day course of arterolane maleate plus piperaquine phosphate is Rs. 130, making it a very affordable option in comparison with artemisinin based treatments.

CONCLUSION:

India has the largest population in the world at risk of malaria. Despite recent success in malaria control globally, sustainability and expansion of these successes is a challenge. Drug resistance has been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease had been eradicated. Use of ACT has shown success in this preventable and treatable disease but resistance to it is emerging, creating the need for new therapies. The fixed dose combination of arterolane (150 mg) and piperaquine phosphate (750 mg) combines a rapidly acting parasiticidal drug with a short acting one that eliminates the residual parasites. It is a completely synthetic drug that ensures regular availability at affordable prices for wide access. The convenient short course treatment encourages compliance. These advantages make this new age antimalarial a welcome

addition to the therapeutic arsenal against *Plasmodium falciparum* malaria.

REFERENCES:

1. Shah NK, Dhillon GPS, Dash AP, Arora U, Meshnick SR, Valecha N. Antimalarial drug resistance of *Plasmodium falciparum* in India: Changes over time and space. Lancet Infect Dis 2011; 11: 57-64.
2. 2.Gargano N, Ubben D, Tommasini S, Bachhieri A, Corsi M, Bhattacharyya PC, *et al*. Therapeutic efficacy and safety of dihydroartemisinin- piperaquine versus artesunate – mefloquine in uncomplicated *Plasmodium falciparum*malaria in India. Malar J 2012; 11: 233.
3. Shah NK. Defining and counting malarial deaths. Indian J Med Res 2012; 135: 270-2.
4. Farooqui HH, Hussain MA, Zodpey S. Malaria control in India: has suboptimal rationing of effective interventions compromised programmed efficiency. WHO South- East Asia J Pub Health 2012; 1: 128-32.
5. Lumb V, Madan R, Das MK , Rawat V, Dev V, Khan W, *et al*. Differential genetic hitichhiking around mutant pfcrt allele in the Indian plasmodium falciparum population. J Antimicrob Chemother 2012; 67:600-8.
6. Bloland P. Drug resistance in malaria. Available from www.who.int/csr/resources/publications/drugresist/malaria.pdf. Last cited on Jan 30, 2013.
7. Sharma YD. Molecular surveillance of drug-resistant malaria in India. Curr Science 2012; 102: 696-703.
8. Das A, Anvikar AR, Cator LJ, Dhiman RC, Eapen A, *et al*. Malaria in India: The center for the study of complex malaria in India. Acta Tropica 2012; 121: 267-73.
9. Singh N, Shukla MM, Chand G, Bharti PK , Singh MP, Shukla MK, *et al*. Epidemic of *Plasmodium falciparum* malaria in Central India, an area where chloroquine has been replaced by artemisinin-based combination therapy. Trans R Soc Trop Med Hyg 2011; 105: 133-9.
10. Kinfu G, Gebre-Selassie S, Fikrie N. Therapeutic efficacy of Artemether- lumefantrine for the treatment of uncomplicated of malaria in northern Ethiopia. Malar Res Treat 2012; 2012: 548710.
11. Anvikar AR , Sharma B, Shahi BH, Tyagi PK, Bose TK, Sharma SK, *et al*. Artesunate-amodiaquine fixed dose combination for the treatment of Plasmodium falciparum malaria in India. Malar J 2012; 11: 97.
12. Anvikar AR, Sharma B, Sharma SK, Ghosh SK, Bhatt RM, Kumar A, *et al*. In vitro assessment of drug resistance in *Plasmodium falciparum* in five States of India. Indian J Med Res 2012; 135:494-9.
13. Saha P, Guha SK, Das S, Mullick S, Ganguly S, Biswas A, *et al*. Comparative efficacies of artemisinin combination therapies in *Plasmodium falciparum* malaria and polymorphism of pfATPase6, pfcrt, pfdhfr and pfdhps genes in tea gardens of Jalpaiguri District, India. Antimicrob Agent Chemother 2012; 56: 2511-7.
14. Fugi MA, Wittlin S, Dong Y, Vennerstrom JL. Probing the antimalarial mechanisms of artemisinin and 0Z277 (arterolane) with nonperoxide isosteres and nitroxyl radicals. Antimicrob Agents Chemother 2010; 54: 1042-6.
15. Gautam A, Ahmed T, Sharma P, Varshney B, Kothari M, Saha N, *et al*. Pharmacokinetics and pharmacodynamics of arterolane maleate following multiple oral doses in adult patients with *Plasmodium falciparum* malaria. J Clin Pharmacol 2011; 51: 1519-28.
16. Snyder C, Chollet J, Santo-Tomas J, Scheurer C, Wittlin S. In vitro and in vivo interaction of synthetic peroxide RBx11160 (0Z277) with piperaquine in Plasmodium models. Exp Parasitol 2007; 115: 296-300.
17. Valecha N, Looareesuwan S, Martensson A, Abdulla SM, Krudsood S, Tangpukdee N, *et al*. Arterolane, a new synthetic trioxolane for treatment of uncomplicated *Plasmodium falciparum* malaria. A phase II multicenter randomized, dose-finding clinical trial. Clin Inf Dis 2010; 51: 684-91.
18. Valecha N, Krudsood S, Tangpukdee N, Mohanty S, Sharma SK, Tyagi PK, *et al*. Arterolane maleate plus piperaquine phosphate for treatment of uncomplicated *Plasmodium falciparum* malaria: a comparative, multicenter, randomized clinical trial. Clin Inf Dis 2012; 55:663-71.
19. Kumar A, Valecha N, Jain J, Dash AP. Burden of malaria in India: Retrospective and prospective view. Am J Trop Med Hyg 2007; 77: 69-78.
20. Yeung S, Damme WV, Socheat D, White NJ, Mills A. Cost of increasing access to Artemisinin combination therapy: the Cambodian experience. Malar J 2008; 7: 84.
21. Davis WA, Clarke PM, Siba PM, Karunajeeva HA, Davy C, Mueller I, *et al*. Cost–effectiveness of artemisinin combination therapy for uncomplicated malaria in children: data from Papua New Guinea. Bulletin of the World Health Organization 2011; 89: 211-20