

Assessment of efficacy and safety of artesunate plus sulfadoxine-pyrimethamine combination for treatment of uncomplicated falciparum malaria

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Received: 19 March 2014

Accepted: 15 April 2014

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ABSTRACT

Background: Resistance of *Plasmodium falciparum* to antimalarial drugs is common in India. World Health Organization (WHO) recommends artemisinin-based combination therapy (ACT) to counter the development of resistance in *P. falciparum*. WHO recommends that ideally antimalarial drug treatment policy or guidelines should be reviewed regularly and updated at least once every 24 months. In consideration to the above recommendation, we planned to conduct the following study. The objective was to determine the efficacy and safety of artesunate + sulphadoxine-pyrimethamine (AS + SP) in patients with uncomplicated *P. falciparum* malaria.

Methods: The study included 60 patients of uncomplicated *P. falciparum*. Each patient received AS + SP as per WHO guidelines. Diagnosis was confirmed by peripheral blood film. All patients were followed-up on days 1, 3, 14, and 28 for detailed clinical and parasitological examination.

Results: Of a total 60 patients, 55 patients were followed-up for 28 days. Remaining 5 patients were lost in follow-up. As per protocol analysis, 91% (50) of patients had demonstrated adequate clinical and parasitological response. Remaining 9% (5) had treatment failure in which 5.5% (3) had late parasitological failure and 3.6% (2) had late clinical failure. In our study, mean parasite clearance time was 45.2 ± 4.2 hrs.

Conclusion: AS + SP is safe and effective drug for the treatment of uncomplicated falciparum malaria. However, the efficacy of this ACT needs to be carefully monitored periodically since treatment failure can occur due to resistance.

Keywords: Uncomplicated *Plasmodium falciparum* malaria, Artemisinin-based combination therapy, Artesunate + sulfadoxine-pyrimethamine

INTRODUCTION

Malaria is one of the major public health problems in India. Around 1.5 million laboratory confirmed cases of malaria are annually reported in India.¹ Around 50% of total malarial cases reported are due to *Plasmodium falciparum*. Resistance of *P. falciparum* to commonly used antimalarial drugs; especially chloroquine is being increasingly recognized in India.² World Health Organization (WHO) recommends the use of Artemisinin-based combination therapy (ACT) to counter the development of resistance in *P. falciparum* to antimalarial drugs and to achieve rapid resolution of parasitemia and morbidity.³

WHO recommends that ideally antimalarial drug treatment policy or guidelines should be reviewed regularly and updated at least once every 24 months.⁴ In consideration to

the above recommendation and lack of availability of Indian data regarding efficacy and safety of AS + SP combination therapy, we planned to conduct following study.

Objective

To determine the efficacy and safety of AS + SP in patients with uncomplicated *P. falciparum* malaria.

METHODS

Study site and design

This study was conducted in Guru Gobind Singh Government hospital (tertiary care hospital), Jamnagar, (Gujarat). It was

an open-labeled single arm prospective study. The primary endpoint was 28th day cure rate and secondary endpoint was parasite clearance time.

Study was conducted according to WHO protocol for "Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria, 2003".⁴

Study was approved by institutional ethical committee (Approval no. MCLJ/IEC/120/2010).

Study was registered in CTRI (Reg NO-->CTRI/2011/091/000047).

Study duration

Study was of 1-year duration. We recruited 60 patients from June 2010 to July 2011.

Study population

Patients with the chief complaint of fever visiting the outpatient department of Guru Gobind Singh Government Hospital (tertiary care hospital), Jamnagar, (Gujarat) were recruited on the basis of the following inclusion and exclusion criteria.

Inclusion criteria

- 1) Age > 12 yrs.
- 2) Slide confirmed cases of *P. falciparum* malaria.
- 3) Patient having a history of fever in preceding 24 hr or having axillary temperature more than 98.2°F.

Exclusion criteria

- 1) Patients with signs or symptoms of severe malaria.⁴
- 2) Patients with other febrile conditions.
- 3) Pregnant or lactating women.

Procedure

After obtaining the written informed consent from patients, a medical history including presenting symptoms, current medication, and previous antimalarial use was obtained. A complete physical examination was performed and case record form was completed for each patient. Clinical history, examination, and other investigations all were recorded. Blood was collected for parasitology.

Efficacy of ACT was checked by looking to treatment outcome.

Treatment outcome were classified according to WHO guidelines into early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF) and adequate clinical and parasitological response (ACPR).⁵

ETF

Development of danger signs or severe malaria on day 1, 2, or 3, in the presence of parasitemia; parasitemia on day 2 higher than on day 0, irrespective of axillary temperature; parasitemia on day 3 with axillary temperature > 37.5°C, and parasitemia on day 3, >25% of count on day 0.

LCF

Development of danger signs or severe malaria in the presence of parasitemia on any day between day 4 and day 28 (day 42) in patients who did not previously meet any of the criteria of ETF, and presence of parasitemia on any day between day 4 and day 28 (day 42) with axillary temperature > 37.5°C in patients who did not previously meet any of the criteria of ETF.

LPF

The presence of parasitemia on any day between day 7 and day 28 with axillary temperature < 37.5°C in patients who did not previously meet any of the criteria of ETF or LCF.

ACPR

After treatment, patient does not have a fever or parasitemia until day 28.

Safety of ACT was assessed by recording adverse drug reactions (ADRs) in Central Drugs Standard Control Organization suspected ADR reporting form. ADR was defined as per the definition provided by WHO (1972).⁶ Causality, severity and preventability of ADR were assessed by WHO Causality Assessment Scale,⁷ Hartwig and Siegel Severity Assessment Scale⁸ and Schumock and Thornton Preventability Scale,⁹ respectively.

Sample size

According to the WHO guidelines in the case of a test drug with an expected failure rate lower than 15%, a minimum of 50 patients should be included in order to be representative.⁴ Hence, we included sample size of 60 patients.

Treatment

Patients were given Artesunate + sulfadoxine-pyrimethamine (AS + SP)

- a. Artesunate-100 mg twice a day for 3 days. (40 mg/kg/day).
- b. Sulfadoxine-Pyrimethamine
1500 + 75 mg (25 mg/kg + 1.25 mg/kg) on 1st day as a single dose.

Follow up

All the patients were followed-up on days 1, 3, 14, and 28. On each day, in addition to physical examination, blood smear for malaria parasites were also obtained.

Statistical analysis

Analysis was performed by using SPSS version 17. Parasite clearance time was assessed by survival analysis using Kaplan-Meir method.

RESULTS

A total of 60 patients having slide positive falciparum malaria were recruited from Guru Gobind Singh Government Hospital (Tertiary Care Centre), Jamnagar, Gujarat during a period of 1 year (June 2010-July 2011). Baseline demographic characteristics of the study population are shown in Table 1. Five patients were lost to follow-up as they migrated to other regions.

As per protocol analysis, 91% (50) of patients had demonstrated ACPR. Remaining 9% (5) had treatment failure in which 5.5% (3) had LPF, and 3.6% (2) had LCF (Figure 1).

Table 1: Demographic and clinical characteristics of patients on inclusion (n=60).

	Number of patients
Gender	
Male	37
Female	23
Age category (years)	
12-30	23
31-60	34
>60	3
Patients with fever on day 0 (Percentage)	100

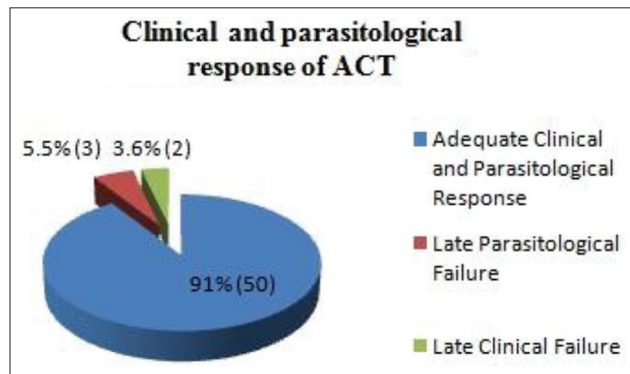


Figure 1: Artemisinin-based combination therapy treatment outcome.

- Two of LPF cases showed the presence of parasitemia on 28th day without any signs or symptoms and the remaining one case showed the same features on day 14th.
- The two LCF cases showed the presence of parasitemia and axillary temperature > 98.5°F on day 10 and 12, respectively. They were prescribed a 7 days course of oral quinine and doxycycline.
- In our study, mean parasite clearance time was 45.2 ± 4.2 hrs.

Only 5.5% (3) patients experienced adverse events mainly in the form of nausea, vomiting, and headache. WHO causality assessment scale revealed all three ADRs as probable. According to Hartwig and Siegel severity assessment scale, two ADRs were mild and one was moderate. All three ADRs were not preventable by Schumock and Thornton preventability scale.

DISCUSSION

In India, ACT has been introduced as first line treatment for uncomplicated *P. falciparum* malaria, due to widespread resistance to chloroquine.¹ ACT recommended by the national program is AS + SP, which is highly effective against *P. falciparum* malaria. Recent studies from western Cambodia have reported a decline in the efficacy of ACT.^{10,11} Therefore, WHO recommends that antimalarial drug treatment policy guidelines should be reviewed regularly and updated at least every 24 months. Hence, based on the above recommendation, we conducted this study to determine the efficacy of ACT (AS + SP) in our region.

Efficacy of AS + SP in our study population was 91%, which is comparable to study done by Mockenhaupt et al. having 94% efficacy.¹² Majority of the studies¹³⁻¹⁵ have reported efficacy in the range of 99-100%, but an efficacy of less than 85% has also been reported in very few studies.^{16,17} The variation in the efficacy observed by us might be due to reason that the majority of these studies was mainly conducted in African subcontinents. Over and above comparable data of efficacy of AS + SP from India is lacking.

It was observed during the course of our study, that parasitemia appeared on day 28, in two patients of the three LPF cases. Parasitemia was not associated with fever or other symptoms of malaria. Since analysis of the parasite genotypes was not performed, it was not possible to determine whether these were new infection, or recrudescence. It is possible that the observed parasitemia on day 28 could be re-infection rather than recrudescence.

Few studies have reported the parasite clearance time in patients receiving AS + SP antimalarial therapy. We observed a parasite clearance time in the range of 41-48 hrs, which is comparable to study done by Ayede et al.¹⁸

Occurrence of only few mild adverse events during the course of AS + SP supports the facts that, it is a safe and

well-tolerated antimalarial therapy for uncomplicated *P. falciparum* malaria.

Other ACT's available in India at present are fixed dose combinations (FDC) of artemether + lumefantrine and blister pack of artesunate + mefloquine.¹ Studies from North Eastern states of India on efficacy of FDC of artemether + lumefantrine reported 98% in Orissa and 100% in Assam, with a good tolerability and very few side effects.¹⁹ WHO guidelines suggest 80 mg artemether + 480 mg lumefantrine (single tablet) twice a day for 3 days, which approximately costs 160 Indian national rupees. Advantage of this combination is that lumefantrine is not available as monotherapy so the chance of developing resistance to this ACT is very low.³ In contrast, resistance to AS + SP is likely to worsen with continued widespread use of sulfadoxine + pyrimethamine (SP) and cotrimoxazole (trimethoprim + sulfamethoxazole) as a monotherapy.³

The cost of AS + SP combination therapy is approximately 120 Indian national rupees, also it is available free of cost under National Vector Borne Disease Control Programme, India. Hence considering the high cost of artemether + lumefantrine therapy, (AS + SP) should be continued as first line therapy for uncomplicated *P. falciparum* malaria and artemether + lumefantrine can be used as an alternative second line treatment.

CONCLUSION

AS + SP is safe and effective drug for the treatment of uncomplicated *P. falciparum* malaria in India. However, the efficacy of this ACT needs to be carefully monitored periodically in different regions of our country, since treatment failure can occur due to resistance.

ACKNOWLEDGMENTS

The authors are grateful to Dr. H.R. Trivedi Professor and Head, Department of Pharmacology, Shri M. P. Shah Medical College, Jamnagar, Dr. Jiyo Chacko 3rd year postgraduate student in MD Pharmacology and all the staff members of Department of Pharmacology.

Funding: None

Competing interests: None declared

Ethical approval: The study was approved by the institutional ethical committee (Approval no. MCLJ/IEC/120/2010)

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doi: 10.5455/2319-2003.ijbcp20140609

Cite this article as: Goyal YN, Bhansali NB, Solanki KC, Mistry RA, Singh AP. Assessment of efficacy and safety of artesunate plus sulfadoxine-pyrimethamine combination for treatment of uncomplicated falciparum malaria. *Int J Basic Clin Pharmacol* 2014;3:465-9.