



Comparative efficacy and safety of sulphadoxine-pyrimethamine and artesunate/pyrimethamine-sulphadoxine in the treatment of acute uncomplicated Plasmodium falciparum infection in Osogbo, southwest, Nigeria.

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Objectives of the study.

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- To determine the level of effectiveness and resistance development to sulphadoxine-pyrimethamine in Osogbo southwest, Nigeria.
- To determine the comparative efficacy of sulphadoxine-pyrimethamine and sulphadoxine-pyrimethamine/artesunate combination.
- To determine the gametocyte carriage rate as a prognostic factor to resistance development and transmission rate in patients treated with sulphadoxine-pyrimethamine and sulphadoxine-pyrimethamine/artesunate combination.
- To determine the effects of pharmacokinetic profile on the observed pharmacodynamic effects of sulphadoxine-pyrimethamine and sulphadoxine-pyrimethamine/artesunate
- To determine the dose – concentration effects relationship as one of the determinant factors for genetic mutations in the resistant strains of plasmodium parasite.



Patients and Methods

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- One hundred and sixty children of both sex within the age of 12months – 120months were recruited into this study.
- Fever $> 37.5^{\circ}\text{c}$; Pure Plasmodium falciparum parasite density $>2000 - \leq 100,000/\mu\text{L}$ of blood, determined by microscopy of Geimsa stained thick blood smears.
- Pre-treatment randomisation into the two treatment groups was single blinded to minimize any bias in the treatment allocation.
- Seventy-nine (79) patients in treatment A had (SP) sulphadoxine-pyrimethamine; Eighty-one(81) patients in treatment B had SP/artesunate.
- History of ingestion of any antimalarial drugs or treatment with drugs of study within past 4weeks, drug induced haemolysis, G-6-PD def., SCD, are exclusion criteria.
- Sixty out of 160 children, 29 from group A and 31 from group B (**Older Patients that can withstand blood sampling procedure**) were randomly selected into electrocardiographic and pharmacokinetic studies to determine the kinetic profile of the drugs of study.
- Clinical, haematological, biochemical assessment (FBC, LFTs, E&U and Creatinine) were done for all patients on D0,D3, D7, D14 and D28. Filter paper samples and blood smears collected on D0 –D3,D7, D14, D21 & D28 for PCR analysis and parasite quantification.



Methods continued.

- Drugs of study were administered by the physician on D0 - 25mg/kg sulphadoxine-2.5mg/kg pyrimethamine as single dose for Gp. A; and D0-SP as in gp. A and 4mg/kg artesunate on D0-D2 to Patients in Gp. B. They were followed-up for 14 and 28 days according to WHO protocol.
- Electrocardiographic studies using 12lead ECG Machine were recorded at 0hr, 4hrs, 12hrs, 24hrs, 36hrs 48hrs, 72hrs, 96hrs, 196hrs and 336hrs.for all the 60 patients in the two treatment groups.
- Fifteen patients from each group were randomly selected for the pharmacokinetic study. Plasma, red cell, filter-paper and saliva samples will be collected at -0hr, ½hr, 1hr, 2hrs, 4hrs, 6hrs, 24hrs, 48hrs, 72hrs, 96hrs, 196hrs and 336hrs.
- PCR analysis to determine adequate clinical and parasitological cure and failures, and determine specific mutations in resistance strains.
- Electrocardiographic assessment by independent observer to confirm any abnormalities.
- Pharmacokinetic analysis by HPLC using different elution methods to determine concentration differences in various biological samples.



Results (1)

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- This study is ongoing, 92 patients have been recruited so far. Forty-five (45) patients treated with SP, 47 patients treated with SP/AS. 4 patients 2 from each group, were lost to follow-up.
- Eighty-two (82/88) completed D14 follow-up, 73 (73/88) completed D28 follow-up, 6 patients failed treatment before D14.
- 15 patients failed the treatment, 10 of which were treated with SP, 5 of which were early treatment failures (ETF) and 5 late treatment failures (LTF) and 5 treated with SP/AS, 3 failures on D21 and 2 failures on D28, were all late treatment failures.
- Cure rates on D14 and D28 with SP were 86.1% and 76.7%, and cure rates on D14 and D28 with SP/AS were 100% and 88.9%.
- Failure rate on D14 was 13.9%, and D28 was 23.3% for patients treated with SP, while failure rate for SP/AS was 11.1% on D28.
- Failed cases were treated with artemether/lumefantrine combination (Coartem®) all responded well no recrudescence after D28.
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Results (2)

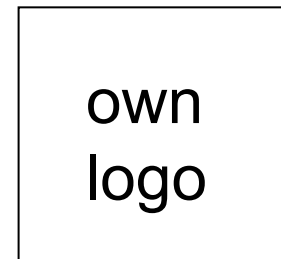
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- Parasite clearance time for was 3days \pm 1.0 for SP, while it was 1.5days \pm 0.7 for SP/AS. $p < 0.05$
- Fever clearance time for SP was 3.5days \pm 1.5 and 1.8days \pm 0.9. $P < 0.05$
- Mean D0 PCV for patients treated with SP was 36% while that of patients treated with SP/AS was 35.0%
- The gross mean parasite density GMPD for patients treated with SP was 45685 \pm 1345, while that of patients treated with SP/AS was 56490 \pm 2278.





Discussion & Conclusions



- Preliminary findings shows that SP resistance is on the increase in southwest Nigeria.
- SP/AS may be a combination therapy that can be explored in other to prolong the clinical half-life of SP.
- In cases where patients react to amodiaquine as haemolysis or toxic hepatitis SP/AS combination may serve as an alternative.
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Future perspectives

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- The electrocardiographic study and the pharmacokinetic study are yet to be concluded.
- PCR analysis is still ongoing,
- Recruitment exercise is also still on going.