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Clinical Safety Profiles of Artesunate and Amodiaquine in Combination with Sulphadoxine-Pyrimethamine for the Treatment of Uncomplicated *Plasmodium Falciparum* Malaria in Children

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Abstract: ***Clinical symptoms serve strong indicators for clinical recoveries and the safety of antimalarials. The present study evaluated the safety of Artesunate + Sulphadoxine - Pyrimethamine (AT+SP) and Amodiaquine + Sulphadoxine Pyrimethamine (AQ+SP) combination therapies in the treatment and recovery trends of eight different clinical symptoms. The study was carried out in malaria holo-endemic settlements in northern Nigeria between July - December 2013 on 313 children with uncomplicated Plasmodium falciparum malaria. Preliminary investigations show that malaria was accompanied by high clinical symptoms (> 60%) in both drug treatment groups at enrolment. There were no drug contraindication on abdominal pain, diarrhea, insomnia and prurities as inferred from the progressive symptom recoveries throughout follow-up period. However, signs of drug adverse effects were expressed for dizziness, headache, and nausea and vomiting, inferred from symptom upsurge within 3 days. In general, the regression trend lines indicate 4 - 5 days mean symptom resolution period, except headache which extended to 5 - 6 days. In conclusion, both AT + SP and AQ + SP could be adjudged safe based on rapid symptom resolution and the short relapse of triggered contraindications in few patients.***

Keywords: malaria, clinical, safety, recoveries, antimalarial

1. Introduction

Plasmodiasis, commonly termed malaria (Italian: *mala* = bad, *aria* = air) has remained a serious health threat to over 24 million children in the tropics [20]. Previous efforts to combat the disease were constrained by the decline in drug efficacy due to resistant *Plasmodium* strains and the drug adverse effects. The history of antimalarials is replete with cases of adverse effects; Chloroquine was banned because of prurities and retinal toxicity [2], [5], [6] and [18] while Amodiaquine usage declined as a result of its severe adverse reactions such as agranulocytosis and hepatoxicity [9], [10] and [3].

Artemisinin-containing combination therapy (ACT) is the World Health Organization (WHO) recommended first-line treatment of acute uncomplicated *Plasmodium falciparum* malaria [25]. Therefore, it has become mandatory to use combination therapy in response to drug resistance, as veritable options like Artemether-Lumefantrine (coartem), Artesunate + Amodiaquine, Artesunate + Mefloquine, Artesunate + Sulphadoxine-pyrimethamine, and Amodiaquine + Sulphadoxine-Pyrimethamine which have recently been the exclusive choice of medical experts in the treatment of malaria [8], [19],[20], [21] and [17]. Besides better efficacy, drug safety is one of the greatest challenges to medical experts and parasitologist, the difficulty the lack of effective assessment tool and standard methodology. Clinical, hematological and biochemical responses offers the best alternative for effective evaluation of drug safety in treated patients [7] and [24]. This study evaluated the clinical safety profiles of Artesunate + Sulphadoxine-Pyrimethamine and Amodiaquine + Sulphadoxine - Pyrimethamine combination therapies in the treatment of uncomplicated *Plasmodium falciparum* malaria in children.

2. Materials and Methods

2.1 Study Site

The study took place in malaria holo-endemic settlements around Lake-Alau, Borno State, Nigeria (Lat: 12^0N and 13^0N; Long: 11^0E and 13^0E). The peri-urban outpatient primary Health Center at Kayamla caters for 63 village settlements with a combined population of 114,224 heads according to Nigerian National Population Commission, 1991.

2.2 Ethical clearance Recruitment Procedure

Ethical clearance was granted by Borno State Ministry of Health, Nigeria and standard recruitment criteria of clinically apparent uncomplicated malaria, mono-infection and absence of severe malnutrition with measured axillary temperature (≥ 37.5 °C), parasite density (2,000 - 200,000 /µl) and packed cell volume (> 15%) were adopted for the study [20]. A total of 500 children suffering from malaria were enrolled out of which 313 children that finally satisfied the inclusion criteria [20] with 161 and 152 patients in the AQ + SP and AT + SP treatment groups, respectively.

2.3 Experimental Procedure

The clinical profiles were generally assessed directly from the patients and indirectly through their parents by the

clinical officers involved in the study in accordance with [20] and [16].

2.3.1 Antimalarial drug adminisration
The amount of drug given was based on body weight:

2.3.1.1 Group 1, - Artesunate + Sulphadoxine-pyrimethamine (AT+SP)
This group was made up of 152 children treated with the anti-malarial drug, Artesunate + Sulphadoxine-pyrimethamine. Each of the children orally received 4 mg⁄kg body weight artesunate daily for three days and a combined 25 mg⁄kg body weight sulphadoxine and 1.25 mg⁄kg body weight pyrimethamine as single oral dose on the first day of treatment.

2.3.1.2 Group 2, -Amodiaquine + Sulphadoxine – pyrimethamine(AQ+SP)
Amodiaquine + Sulphadoxine - pyrimethamine was orally administered to the second group of 161 children at the dose of 10 mg⁄kg body weights of amodiaquine daily for three days and also a combined 25 mg⁄kg body weight sulphadoxine and 1.25 mg⁄kg body weight pyrimethamine as a single oral dose on the first day of treatment.

2.3.1.3 Drug formulation, dose and treatment regiments are as shown below:

Trade name	Manufacturer	Generic name	Dose/kg body wt.	Course
ARTESUNAT®	Mekophar Pharmaceutical(Ho Chi Minh City, Vietnam)	Artesunate 50 mg (Dihydroartemisinin 1,2-α-succinate)	4 mg	3 days
CAMOQUIN®	Pfizer (Dakar R.P., Senegal)	Amodiaquine hydrochloride 200 mg	10 mg	3 days
MALCIDA®	Juhel (Enugu, Nigeria)	Sulphodoxine 500 mg Pyrimethamine 25 mg	25 mg 1.25 mg	1 day

2.4 Data management and analysis

Data collected were subjected to descriptive statistics using the analytical software Staistix Version 8.0 (Microsoft, 2003). Frequency and percentages were computed for clinical symptoms recorded on follow-up days. Charts were drawn using Microsoft Excel (2003) and regression analysis to compare clinical expressions in the two test drugs (AT+SP and AQ+SP) on children with *P. falciparum*. The coefficient of determination, r^2 shows the speed of symptom clearance with higher values indicating higher time dependence of the symptom and lag in clearance. The point at which the trend line intercepts the x-axis served as estimate of the mean symptom resolution time, while the regression coefficient quantitatively expressed the daily rate of recovery.

3. Results

Fig. 1 indicates logarithmic recovery trend in AT+SP versus AQ+SP treated children. There were no drug contraindication on abdominal pain, diarrhea, insomnia and prurities, based on the progressive symptom resolution. The r^2-values indicated faster resolution of these symptoms by AT+SP (63.38 – 75.40%) than AQ+SP (65.29 – 83.90%) within the specified period of 7 days, while the regression trend lines indicated mean symptom resolution period of 4 - 5 days. Result shows a sharp decrease in abdominal pain from 88.2% - 5.3% after 2 days in AT+SP patients compared to 85.1 - 0.6% on day 3 in AQ+SP patients. Similarly, diarrhoea was resolved from 84.9 - 2.6% after treatment with AT+SP as against 83.9 - 2.5% in AQ+SP; insomnia from 85.7 - 0.7% compared to 72.0 - 1.9% and pruritis from 73.3 - 4.6% as against 64.0 - 5.0% within three days of drug administration. Specifically, mean symptom resolution time (MSRT) was relatively shorter for AT+SP than AQ+SP in respect of abdominal pain (48 vs 72 hr), longer for diarrhea, while both drugs resolved insomnia and prurities in 72 hr. The regression coefficient indicated daily rate of symptom resolution in AT+SP vs AQ+SP by 50.92 versus 50.13%, 47.68 versus 47.84%, 50.22 versus 43.84% and 43.69 versus 39.30% for abdominal pain, diarrhea, insomnia and prurities, respectively.

In contrast, signs of adverse effects were expressed in dizziness, headache, and nausea and vomiting within 3 days, in which despite of the sharp decrease, there was upsurge in these symptoms (Fig. 2). However, the overall results indicated upsurge in dizziness from 10.5% on day 1 to 15.1% on day 2, however, dizziness from 71.7 - 1.3% in AT+SP patients compared to 76.4 - 1.9% obtained with AQ+SP patients within 3 days. There was surge in headache from 4.6 – 17.1% in AT+SP patients and 3.1 - 9.3% in AQ+SP patients as from day 1 to 3; however, headache was resolved from 61.2 at enrolment to 4.6% on the first day compared to 72.7 - 3.1% with AQ+SP. Nausea surged from 3.3 - 6.6% in AT+SP patients and 2.5 - 5.6% in AQ+SP patients, although cases decreased from 85.5 - 4.6% and 88.8 - 2.5% on day, respectively. The result indicated surge in vomiting in AQ+SP patients from 5.6% on day 1 to 7.5% on day 2, however, by day 3 symptom was resolved from 86.2 and 83.9% for AT+SP and AQ+SP at enrolment to 0.7 and 1.2% in AQ+SP, respectively. The r^2-values indicated faster resolution vomiting by AT+SP (64.73%) than AT+SP (65.61%), in contrast to faster resolution of dizziness, headache and nausea by AQ+SP (62.20 - 74.57%) than AT+SP (64.02 - 75.34%). In general, the regression trend lines indicate 4 - 5 days mean symptom resolution period, except headache which extended to 5 - 6 days. Specifically, mean symptom resolution time (MSRT) was relatively shorter for AT+SP than AQ+SP in respect of dizziness (72 versus 96 hr) but longer for headache (120 versus 96 hr). However, in both drugs, nausea was resolved in 72 hr and vomiting in 96 hr. The regression coefficient showed daily rate of symptom resolution in AT+SP versus AQ+SP by 42.04 versus 46.21%, 30.45 versus 38.09%, 48.61 versus 50.35% and 49.45 versus 48.06% for dizziness, headache, nausea and vomiting, respectively.

4. Discussion

Clinical expressions serve as effective drug safety indices in treated patients. In the present study, there were no drug

contraindication on abdominal pain, diarrhea, insomnia and prurities based on continuous recovery pattern. This result agrees with the reports of [11] and [23] on clinical recovery and drug safety. The present result revealed adverse effects on dizziness, headache, nausea and vomiting, with adverse effects on dizziness from AT+SP and on vomiting from AT+SP. Similarly, both drugs triggered headache and nausea but adverse effects were higher from AT+SP than AQ+SP. This result concurs with the reports of [13] who associated 4-aminoquinolines with considerable toxic effects including vomiting and neurotoxicity (headache) in patients treated with Artesunate. In a similar trend, [12] pointed out that clinical symptoms such as nausea, vomiting, anorexia and dizziness in Artesunate treated patients could probably be due to the malaria itself rather than due to the drugs. However, result of the present study recorded symptom upsurge in the face of recovery. There was faster resolution of abdominal pain, diarrhea, insomnia, prurities and vomiting by AT+SP than AQ+SP, which concurs with the findings of [15] and [16] of less frequent toxic effects with the Artemisinins than with other antimalarial agents. Similarly, the higher percentage recovery by AQ+SP from headache and nausea concurs with several reports [22], [7] and [14]. The significant reduction in diarrhea and dizziness also corroborates the reports of [4] and [1]. In conclusion, both AT + SP and AQ + SP could be adjudged safe based on rapid symptom resolution and the short relapse of triggered contraindications in few patients.

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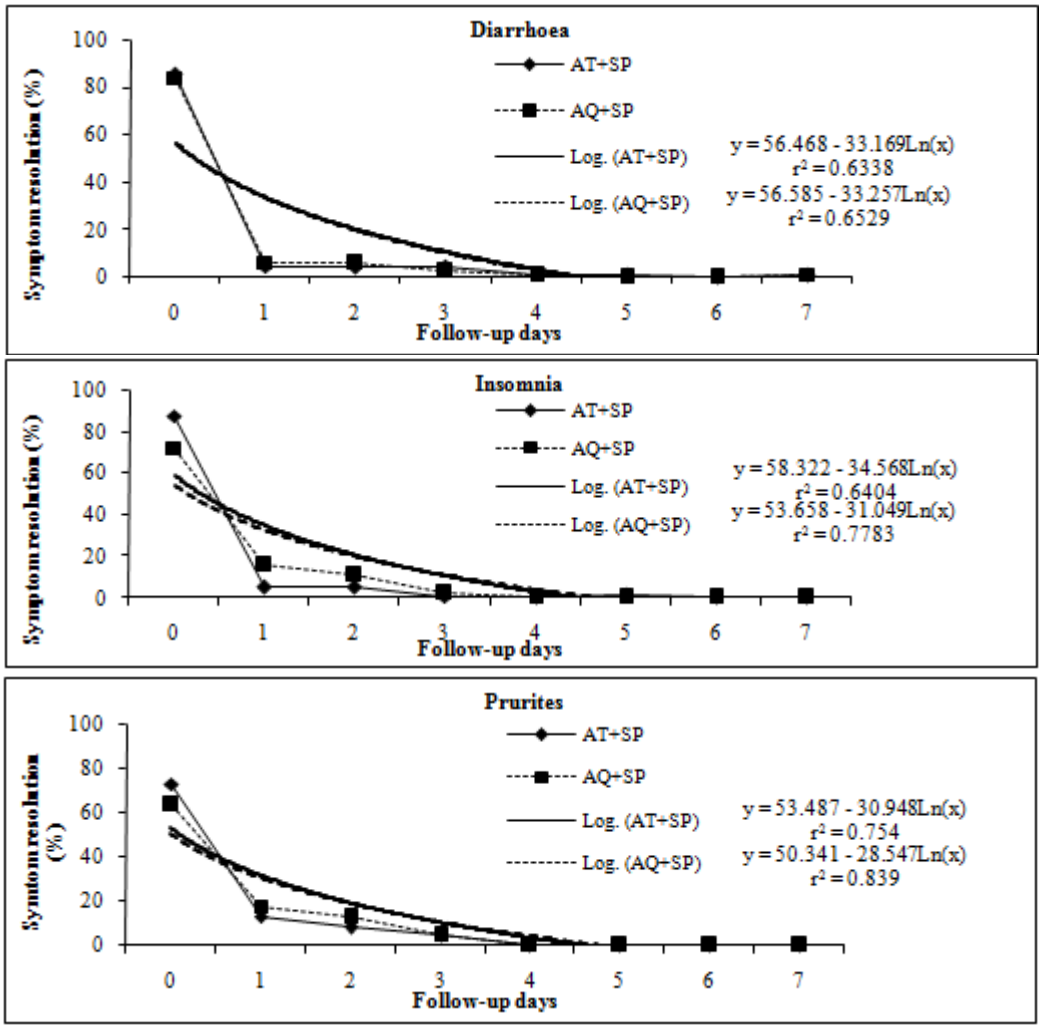


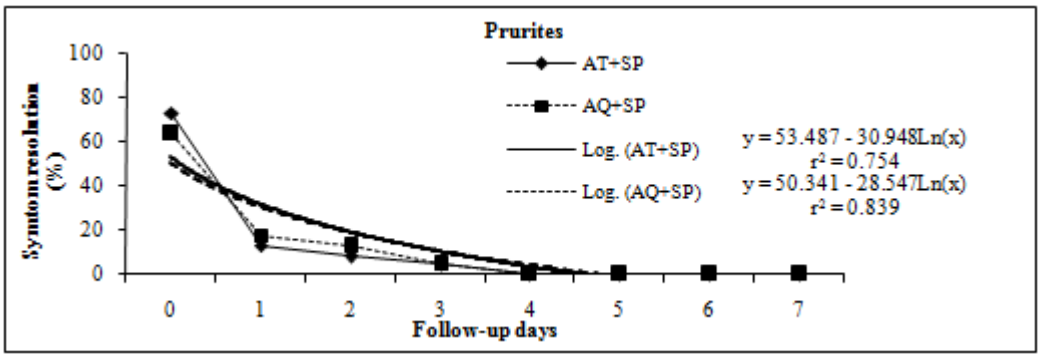
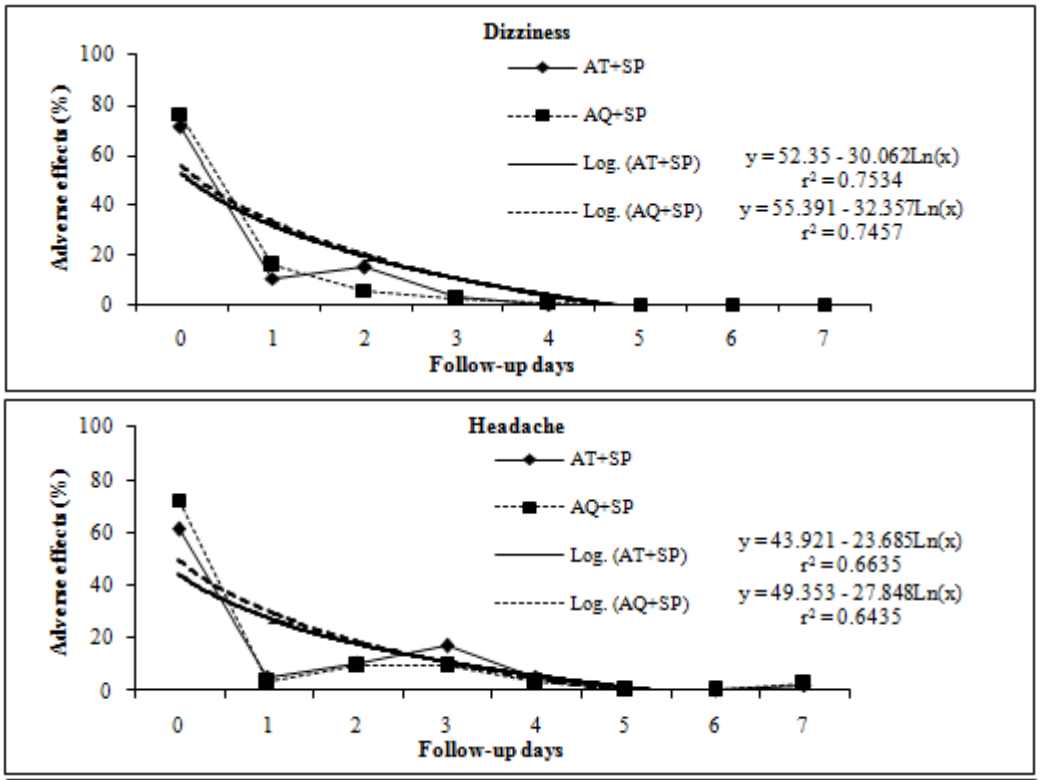


Figure 1: Safety profile of AT+SP and AQ+SP showing no contraindication effects on malaria clinical symptom within a week of drug administration



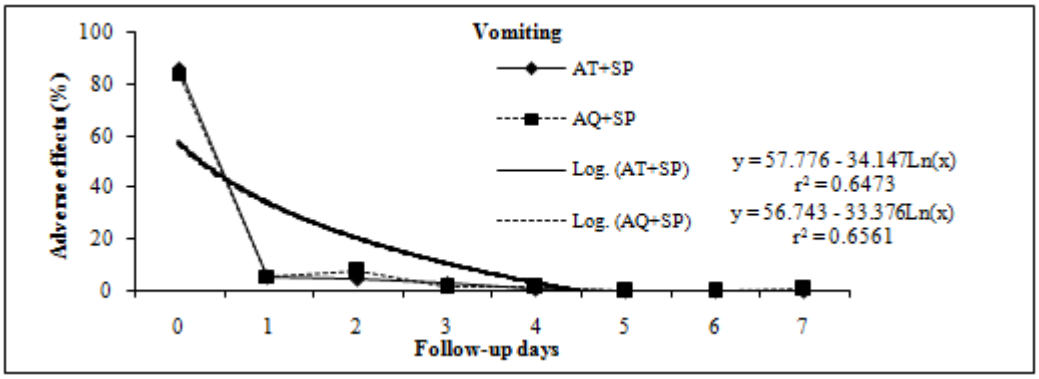


Figure 2: Safety profile of AT+SP and AQ+SP showing signs of adverse effects on some malaria clinical symptom within a week of drug administration