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Comparative Haematological Safety Profiles of AT+SP and AQ+SP for the Treatment of Uncomplicated Plasmodium Falciparum Malaria in Children

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Abstract

Haematological profiles serve as strong indicators of recovery and the safety of antimalarial drugs in children. The present study evaluated the safety of Artesunate + Sulphadoxine-Pyrimethamine (AT+SP) and Amodiaquine + Sulphadoxine-Pyrimethamine (AQ+SP) combination therapies in the treatment on thirteen different haematological and a biochemical parameters. The study was carried out in malaria holo-endemic settlements in northern Nigeria, among 313 children with uncomplicated Plasmodium falciparum malaria randomly selected, between July and September, 2012 using therapeutic efficacy protocols on antimalarial drugs. There were no cases of lympopenia, and recoveries were faster in AT+SP than AQ+SP for leucocytosis (37.5% vs 17.39%), anaemia (82.23% vs 78.03%), thrombocytopenia (90.13% vs 88.20%), monocytosis (30.92% vs 28.01%) and eosinophilia (31.68%) than AQ+SP (18.01%) in 28 days. Conversely, the recoveries from AQ+SP were higher than AT+SP for neutrophilia (32.89% vs 38.45%), and ALT (76.31% vs 78.33%) over 28 days. In contrast, there were slight adverse effects in both drugs on leucopenia, thrombocytosis, neutropenia, lympocytosis and monocytopenia in the range of 1.97 - 20.50% for AT+SP compared to 3.29 - 11.18% for AQ+SP. Except for monocytopenia, the adverse effects due to AT+SP was higher compared to AQ+SP. Both drugs could be adjudged safe based on rapid recoveries with negligible frequency of adverse effects.

Keywords: Haem-safety-profiles, malaria.

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1.0. Introduction

Malaria (Italian: *mala* = bad, *aria* = air) has remained a serious health threat to over 24 million children in the tropics [18, 35]. Previous efforts to combat the disease were constrained by the decline in drug efficacy due to resistant *Plasmodium* strains and the drug adverse effects. Haematological response was proposed as one of the criteria for evaluating safety and therapeutic response [28]. The history of antimalarials is replete with cases of adverse effects on leucocyte [30] neutrophil [19], eosinophil [7] and red blood cells [20]. In response to drug resistance, combination therapy had been recommended as a veritable option and Artemether-Lumefantrine (coartem), Artesunate + Amodiaquine, Artesunate + Mefloquine, Artesunate + Sulphadoxine-pyrimethamine, and Amodiaquine + Sulphadoxine-pyrimethamine have recently been the exclusive choice of medical experts in the treatment of malaria[11,34, 35] and [36, 31]. 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, haematological and biochemical response offers the best alternative for effective evaluation of drug safety in treated patients. This study evaluated the haematological safety profile of Artesunate + Sulphadoxine-Pyrimethamine and Amodiaquine + Sulphadoxine-Pyrimethamine combination therapies in the treatment of uncomplicated *Plasmodium falciparum* malaria in children.

2.0. 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 (National Population Commission, 1991).

2.2. Ethical clearance Recruitment Procedure

Ethical clearance was granted by Borno State Ministry of Health and standard recruitment criteria of clinically apparent uncomplicated malaria, mono-infection and absence of severe malnutrition and measured axillary temperature (≥ 37.5 °C), parasite density (2,000 - 200,000 /µl) and packed cell volume (> 15%) were adopted for the study (World Health Organization, 2003). A total of 500 children suffering from malaria were enrolled out of which 313 children that finally satisfied the inclusion criteria [35] with 161 and 152 patients in the AQ + SP and AT + SP treatment groups, respectively.

2.3. Experimental Procedure

2.3.1. Haematological

Blood for the assessment parasite density was sampled on 0, 1, 2, 3, 4, 7, 14 and 28 by finger pricking, while the venipuncture sample was used for the assessment of Packed Cell Volume on days 0, 3, 7, 14 and 28 as described by WHO (1996). Haematological laboratory analysis was based on the methods by [32,10, 61].

2.3.2. White blood cell count ($x10^9$/µl): Micropipette was used to accurately measure out 20 µl of EDTA anticoagulated blood sample. The blood sample was then diluted in 0.38 ml which haemolyzed the red blood cell leaving only the stained white blood cells. White blood cell was counted microscopically under the x10 objectives using hand tally counter in haemotocytometer ('Neubauer" ruled counting chamber). The total number of white blood cells was then divided by 2 and the figure obtained was further divided by 10 to arrive at the WBC x 10^9 per liter of blood.

2.3.3. Packed cell volume (PCV %): The EDTA anti-coagulated blood sample was centrifuged (Hawksley®) at 12000 (rpm) for 5 minutes and the PCV value was then read-off using a hand held microhaematocrit reader and the values were expressed as percentages [6].

2.3.4. Platelet count ($x10^9/\mu l$): Micropipette was used to accurately measure out 20 µl of EDTA anticoagulated blood sample. The blood sample was then diluted in ammonium oxalate 10 g/l (1% w/v) which haemolyzed the red blood cell. Platelets in the small squares of the haemocytometer were then counted under the objectives of the microscope (x40) using hand tally counter. The actual platelet count was then directly reflected as the platelet count x 10^9 per liter of blood[6].

2.3.5. Differential leucocytes count: Thin blood film was stained for 30 - 45 minutes with 3% Giemsa for the assessment of differential leucocytes. The samples were microscopically examined under the ×100 objectives and neutrophils, lymphocytes, monocytes and eosinophils were directly counted in the field. These were expressed later as the percentage of the total leucocytes count equivalated to 100% [6].

2.4. Biochemical

2.4.1 Alanine-amino-tranferase (ALT): Alanine-amino-transferase was quantitatively determined using Randox Kit (Randox Laboratories Ltd, UK) as described by [33]. Samples of the reagent blank, standard (pyruvat 57 ALT IU/l) and the patients' serum were used for the assessment of the enzyme activity. The serum (0.1 ml) was mixed with 0.5 ml of phosphate buffer solution (100 mmol/L, PH 7.4), containing the substrate L-alanine (200 mmol/L) and α-ketoglutarate (2.0 mmol/L) and then incubated at 37^0C for 30 minutes. Thereafter, a solution (5 ml) sodium hydroxide was added and mixed thoroughly and allowed to stand for 20 minutes at 25^0C. The absorbance was then read against the reagent blank and sample blank in the spectrophotometer (Hg 546) at a wavelength of 505 nm. The absorbance values were then read-off against tabulated values to obtain the corresponding enzymes (ALT) activity in units per liter (U/l), which was recorded for days 0, 3, 7, 14 and 28 during the study.

2.5. Randomization and treatment allocation

The amount of drug given was based on body weight:

2.5.1. 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.

2.5.2. 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. Drug formulation, dose and treatment regiments are as shown in table 1.

2.6. 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 adverse haematological drug effects: leucocytosis and leucopenia (WBC), anemia (PCV), thrombocytosis and thrombocytopenia (platelets), neutrophilia and neutropenia (neutrophils), lympocytosis and lympopenia (lymphocytes), monocytosis and monocytopenia (monocytes), eosinophilia and eosinophenia (eosinophils).

table 1.

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

3.0. Results

Table 1 shows that there here were no cases of lympopenia and recovery from AT+SP was higher for anaemia (Table 2), thrombocytopenia (Table 3) and monocytosis (Table 6) with recovery frequencies of 92.76 - 10.53%, 97.37 - 7.24% and 37.50 - 6.58% than from AQ+SP with 93.02 - 14.99%, 94.41 - 6.21%, 34.78 - 6.77%, respectively, over 28 days. Conversely, though, Table 4 indicates that recoveries from AQ+SP were higher than AT+SP for neutrophilia (36.18 - 3.29% vs 42.80 - 4.35%); while in Table 7, recovery from eosinophilia was irregular but faster in AT+SP (36.18 - 4.50%) than AQ+SP (29.81 - 11.80%) in 28 days. The results in Table 8 similarly indicated higher recoveries in ALT from AQ+SP (83.23 - 4.97%) than AT+SP (77.63 - 1.32%). These translate to recoveries as faster in AT+SP than AQ+SP for leucocytosis (37.5% vs 17.39%), anaemia (82.23% vs 78.03%), thrombocytopenia (90.13% vs 88.20%), monocytosis (30.92% vs 28.01%) and eosinophilia (31.68%) than AQ+SP (18.01%) in 28 days. Conversely, the recoveries from AQ+SP were higher than AT+SP for neutrophilia (32.89% vs 38.45%), and ALT (76.31% vs 78.33%) over 28 days.

Result in Table 1 shows that AT+SP and AQ+SP triggered leucopenia from 9.94 - 20.50% and 3.29 - 8.55% in children. Similarly, Tables 3 - 6 indicated adverse effects from AT+SP and AQ+SP with upsurge in thrombocytosis (0 - 9.86% vs 0 - 5.5%), neutropenia (0 - 6.23% vs 0 - 3.37%), lympocytosis (0 - 1.97% vs 0 - 1.86%) and monocytopenia (4.61 - 7.89% vs 4.99 - 11.18%) in the respective drugs. Except for monocytopenia the adverse effects due to AT+SP was higher compared to AQ+SP.

4.0. Discussion

Haematological profiles serve as effective drug safety indices in treated patients [1]. The present result depicts very high recovery in some key haematological and biochemical parameters namely, anaemia, thrombocytopenia and liver disorders (ALT) in 82.2%, 90.1% and 76.3% for AT + SP and 78.2%, 88.2% and 78.3% for AQ + SP, respectively. *P. falciparum* infection is believed to be a major contributory factor to the etiology of anemia in malaria endemic areas [23, 13]. Malaria parasites invade and exploit red blood cells during their asexual expansion [21] and the direct destruction of parasitized red blood cells through immune mechanisms destroys both parasitized and non-parasitized red cells or the suppresses the bone marrow[14, 13].

Thrombocytopenia is identified as a key indicator of malaria (parasitaemia) in febrile patients and the report further drew a parallel trend in thrombocytopenia with parasitemia [5,8,15]. The trend of decreasing platelet count with increasing levels of parasitemia observed in this study has been previously noted for *P. falciparum* [22,25, 8]. The present study found 95.9% cases of thrombocytopenia at enrolment which concurs with the value of 93% [17] or 89.0% [29].Similarly, [8, 24] further reported that platelet count showed the strongest association and had the greatest predictive power for malaria among all blood parameters.

The present result also shows that rate of hepatic clearance was faster in patients treated with AT + SP than those that received AQ + SP with higher mean values at the end of 28 days. This could be mainly because Amodiaquine is retained longer in the liver and further stresses the liver cells resulting in an associated agranulocytosis and hepatitis [24]. Furthermore, [2] pointed out that liver function tests in patients disposed to drug shows the effects of drugs on

the liver. Abnormal liver enzyme levels may signal liver damage [27] and liver enzyme alteration may be the accompanying biochemical picture in patients [9]. The pathophysiology of malarial infection on liver relates to the sporozoites which invade hepatocytes after which merozoites are released and invade erythrocytes and the repeated cycles of erythrocyte invasion and rupture lead to organ dysfunction [3, 26].

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Table 1 Adverse effects of AT + SP and AQ + SP on leucocytes (WBC x 10^9/L) during follow-up periods (0 – 28 days)

Follow-up days	Adverse effects	AT + SP	AQ + SP
At enrolment	Leucocytosis	66/152 (43.42%)	37/161 (22.98%)
	Leucopenia	5/152 (3.29%)	16/161 (9.94%)
Day 3	Leucocytosis	30/152 (19.74%)	27/161 (16.77%)
	Leucopenia	6/152 (3.95%)	22/161 (13.66%)
Day 7	Leucocytosis	16/152 (10.53%)	4/161 (2.48%)
	Leucopenia	9/152 (5.92%)	13/161 (8.07%)
Day 14	Leucocytosis	14/152 (9.21%)	10/161 (6.21%)
	Leucopenia	9/152 (5.92%)	27/161 (16.77%)
Day 28	Leucocytosis	9/152 (5.92%)	9/161 (5.59%)
	Leucopenia	13/152 (8.55%)	33/161 (20.50%)

Reference ranges (Taha *et al*.,2007)**:** Leucocytosis, > 13 x 10^9/L; Leucopenia, < 4.5 x 10^9/L

Table 2 Adverse effects of AT + SP and AQ + SP on PCV (anaemia, %) during follow-up periods (0 – 28 days)

Follow-up days	Adverse effects	AT + SP	AQ + SP
At enrolment	Anaemia	141/152 (92.76%)	153/161 (93.03%)
Day 3	Anaemia	135/152 (88.82%)	137/161 (85.09%)
Day 7	Anaemia	87/152 (57.24%)	93/141 (57.76%)
Day 14	Anaemia	64/152 (42.11%)	65/161 (40.37%)
Day 28	Anaemia	16/152 (10.53%)	24/161 (14.91%)

Reference ranges (Taha *et al*.,2007): PCV < 33% (Anaemic)

Table 3 Adverse effects of AT + SP and AQ + SP on platelets (x 10^9/µl) during follow-up periods (0 – 28 days)

Follow-up days	Adverse effects	AT + SP	AQ + SP
At enrolment	Thrombocytosis	0/152 (0%)	0/161 (0%)
	Thrombocytopenia	148/152 (97.37%)	152/161 (94.41%)
Day 3	Thrombocytosis	0/152 (0%)	0/161 (0%)
	Thrombocytopenia	77/152 (50.66%)	65/161 (40.37%)
Day 7	Thrombocytosis	1/152 (0.66%)	2/161 (1.24%)
	Thrombocytopenia	24/152 (15.79%)	33/161 (20.50%)
Day 14	Thrombocytosis	1/152 (0.66%)	2/161 (1.24%)
	Thrombocytopenia	18/152 (11.84%)	22/161 (13.66%)
Day 28	Thrombocytosis	15/152 (9.86%)	9/161 (5.59%)
	Thrombocytopenia	11/152 (7.24%)	10/161 (6.21%)

Reference ranges (Taha *et al*., 2007)**:** Thrombocytosis, > 400,000 x 10^9/µl;
Thrombocytopenia, < 150,000 x 10^9/µl

Table 4 Adverse effects of AT + SP and AQ + SP on neutrophils (%) during follow-up periods (0 – 28 days)

Follow-up days	Adverse effects	AT + SP	AQ + SP
At enrolment	Neutrophilia	55/152 (36.18%)	69/161 (42.86%)
	Neutropenia	0/152 (0%)	0/161 (0%)
Day 3	Neutrophilia	40/152 (26.32%)	23/161 (14.86%)
	Neutropenia	0/152 (0%)	0/161 (0%)
Day 7	Neutrophilia	19/152 (12.50%)	10/161 (6.21%)
	Neutropenia	3/152 (1.97%)	4/161 (2.84%)
Day 14	Neutrophilia	13/152 (8.55%)	9/161 (5.59%)
	Neutropenia	4/152 (2.63%)	6/161 (3.73%)
Day 28	Neutrophilia	25/152 (16.44%)	7/161 (4.35%)
	Neutropenia	1/152 (0.66%)	9/161 (5.59%)

Reference ranges (Taha *et al*.,2007): Neutrophilia, >65%; Neutropenia, < 30%

Table 5 Adverse effects of AT + SP and AQ + SP on lympocytes (%) during follow- up periods (0 – 28 days)

Follow-up days	Adverse effects	AT + SP	AQ + SP
At enrolment	Lympocytosis	0/152 (0%)	2/161 (1.20%)
	Lympopenia	78/152 (51.32%)	96/161 (59.62)
Day 3	Lympocytosis	1/152 (0.65%)	1/161 (0.62%)
	Lympopenia	35/152 (23.02%)	51/161 (31.67%)
Day 7	Lympocytosis	1/152 (0.65%)	3/161 (1.86%)
	Lympopenia	21/152 (13.82%)	28/161 (17.39%)
Day 14	Lympocytosis	3/152 (1.97%)	0/161 (%)
	Lympopenia	13/152 (8.55%)	33/161 (20.49%)
Day 28	Lympocytosis	0/152 (0%)	0/161 (0%)
	Lympopenia	9/152 (5.92%)	23/161 (14.28%)

Reference ranges (Taha *et al*., 2007)**:** Lympocytosis, > 60%; Lympopenia, < 30%

Table 6 Adverse effects of AT + SP and AQ + SP on monocytes (%) during follow-up periods (0 – 28 days)

Follow-up days	Adverse effects	AT + SP	AQ + SP
At enrolment	Monocytosis	37/152 (24.34%)	56/161 (34.78%)
	Monocytopenia	7/152 (4.61%)	8/161 (4.99%)
Day 3	Monocytosis	24/152 (15.80%)	27/161 (16.77%)
	Monocytopenia	12/152 (7.89%)	16/161 (10.53%)
Day 7	Monocytosis	22/152 (14.50%)	23/161 (14.29%)
	Monocytopenia	10/152 (6.57%)	18/161 (11.18%)
Day 14	Monocytosis	24/152 (19.21%)	25/161 (15.53%)
	Monocytopenia	11/152 (7.24%)	17/161 (10.56%)
ay 28	Monocytosis	18/152 (11.84%)	27/161 (6.77%)
	Monocytopenia	3/152 (1.97%)	8/161 (4.97%)

Reference ranges (Taha *et al*.,2007): Monocytosis, > 9%; Monocytopenia, < 1%

Table 7 Adverse effects of AT + SP and AQ + SP on eosinophils (%) during follow-up periods (0 – 28 days)

Follow-up days	Adverse effects	AT + SP	AQ + SP
At enrolment	Eosinophilia	55/152 (36.18%)	48/161 (29.81%)
	Eosinophenia	0/152 (0%)	0/161 (0%)
Day 3	Eosinophilia	30/152 (19.74%)	49/161 (30.43%)
	Eosinophenia	0/152 (0%)	0/161 (0%)
Day 7	Eosinophilia	31/152 (20.39%)	36/161 (22.36%)
	Eosinophenia	0/152 (0%)	0/161 (0%)
Day 14	Eosinophilia	19/152 (12.50%)	23/161 (14.28%)
	Eosinophenia	0/152 (0%)	0/161 (0%)
Day 28	Eosinophilia	16/152 (10.52%)	19/161 (11.80%)
	Eosinophenia	0/152 (0%)	0/161 (0%)

Reference ranges (Taha *et al*.,2007): Eosinophilia, > 4%; Eosinophenia, 1 < %

Table 8 Adverse effects of AT + SP and AQ + SP on ALT (U/L) during follow-up periods (0 – 28 days)

Follow-up days	Adverse effects	AT + SP	AQ + SP
At enrolment	Abnormal	118/152 (77.63%)	134/161 (83.23%)
Day 3	Abnormal	32/152 (21.05%)	39/161 (24.22%)
Day 7	Abnormal	23/152 (15.13%)	45/161 (27.95%)
Day 14	Abnormal	3/152 (1.97%)	20/161 (12.42%)
Day 28	Abnormal	2/152 (1.32%)	8/161 (4.97%)

Reference ranges (Llorenc *et al*., 2006): ALT > 40 U/L (abnormal)