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Safety profile of Artemether-Lumefantrine combination therapy among children below ten years in the university of benin teaching hospital, Benin City, Nigeria

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ABSTRACT

Following the change in malaria policy in the year 2005, the safety profile of Artemether-Lumefantrine was assessed among children below ten years that presented with uncomplicated malaria in the University of Benin Teaching Hospital, Benin City, Nigeria, between January and December 2007. Designed questionnaire were systematically distributed among one thousand five hundred children that were recruited for the study. The children were aged 4.8±3.14years, body weight 21±4.12kg. At therapeutic doses 1399 [93.27%] patients reported with nine systemic and forty-one types of side effects. Body weakness [32.00%] was the most frequently reported, followed by Dizziness [31.00]%. Other side-effects were fever [9.00%], insomnia [5.00%], itching [0.13%], blurred vision [5.92%], increased heart beat [3.42%], stomach upset [0.10%] , headache [2.62%], confusion\anxiety [1.09%], diarrhea [0.90%], loss of appetite [3.07%], convulsion [0.16%], change in urine color [3.55%], ear pain [0.12%]. The side-effects were dependent on the ages of the patients [p<0.05, Chi-square] and most frequent between ages 8 and 10years. None was hospitalized as a result of side-effect no death recorded during therapy. It was observed that 0.73% reported with severe malaria and they were treated with either quinine or artemether at 10mg\kg and 1.6mg\kg respectively. 2.27% had spinal meningitides and were treated with penicillin or cephalosporin class of antibiotic. Artemether-Lumefantrine was safe and well tolerated in this study, it is therefore recommended for the treatment of uncomplicated malaria children below ten years.

Key words: Malaria, Artemether-Lumefantrine, Safety, Children,

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INTTRODUCTION

Malaria infection still remains a burden particularly among children in the sub-Saharan Africa. Data of annual 300-500 million clinical cases worldwide and ninety percent mortality in tropical Africa demand much attention even with the introduction of combination therapies [1].

Resistance to antimalarial drugs has been observed as one of the greatest problems in the control of malaria in Africa [2]. This drawback cut across most antimalarials irrespective of their classes. However, the value of malarial therapy using combinations of drug has been identified as a strategic and viable option in improving efficacy, and delaying development and selection of resistance [3]. It is quite interesting to note that drugs may not be entirely safe in all patients, even when they have been reported safe in some regions they could still be influenced by sex, age, race, disease, body weight, and pharmaceutical dosage forms. The risk associated with their use in pregnancy and children below five years as the most afflicted groups in malarial scourge demands much attention in order to reduce the burden [4]. Meanwhile, for a drug considered to be safe, its side-effects should be within the tolerable limit of the individual. Ideally, rare cases of toxicities and adverse reactions are expected to occur during post-marketing surveillance.

Due to the limited data on the safety of Artemether-Lumefantrine, it became necessary to assess the safety profile in children below 10years that reported with uncomplicated malaria in the University Benin Teaching Hospital, Benin City. Nigeria.

MATERIALS AND METHODS

University of Benin Teaching Hospital is a tertiary hospital located in the South-South geographical area of Nigeria. It serves as a clinical centre for the residents of Benin City and neighboring states. In the year 2007 the centre received a donation of seven thousand doses of Artemether-Lumefantrine (Coartem®, Novartis: 20 mg artemether/120 mg lumefantrine tablets), from the Federal Ministry of Health to fulfill the adoption of the 2005 policy for malaria treatment [5]. The doses were given out freely to patients in order to reduce the burden of malaria maximally. One thousand five hundred children were systematically randomized to assess the safety in children between 2years and 10years that presented with uncomplicated malaria. Questionnaire was designed from previous reports that had some major adverse effects associated with the clinical use of drugs [6].

Patients recruited for the study were those that had parasite density of 10,000/µl–200,000/µl, temperature greater than or equal to 37.5^0C, history of allergy to any of the drugs in the combination. The structured questionnaires were administered face-face interviews for non-literate parents\ guardians and self-administered by the literates. The questionnaires were filled and returned to pharmacy unit as the collection centre. Those that had one or more of the general danger signs of severe or complicated malaria, mixed infection, severe malnutrition, febrile condition caused by diseases other than malaria, severe diseases such as HIV\AIDS, tuberculosis, history of allergy to Artemether-Lumefantrine were excluded form the study after obtaining an ethical consent from the institution. Other patients excluded during follow-up were those that had other antimalarial drugs outside the Artemether-Lumefantrine, emergence of any

concomitant febrile illness that interfered with outcome classification and withdrawal of informed consent.

Statistical Analysis

Data collected were entered into Microsoft excel, SPSS version 11.0 [SPSS, Inc. Chicago, IL]. Where necessary, data were computed as frequency and percentage. Continuous data were expressed as mean±standard deviation, while categorical data were analyzed using Chi-square test, *p*-values less than 0.05 were regarded as significant.

RESULTS

Among the one thousand five hundred randomly selected children, they were male: female ratio 1:1.6. The children were aged 4.8±3.14years, body weight 21±4.12kg. At therapeutic doses 1399 [93.27%] patients reported with nine systemic and forty-one types of side effects. Body weakness [32.00%] was the most frequently reported, followed by Dizziness [31.00%]. Other side-effects were fever [9.00%], insomnia [5.00%], itching [0.13%], blurred vision [5.92%], increased heart beat [3.42%], stomach upset [0.10%] , headache [2.62%], confusion\anxiety [1.09%], diarrhea [0.90%], loss of appetite [3.07%], change in urine color [3.55%], ear pain [0.12%]. The side-effects were dependent on the ages of the patients [$p<0.05$, Chi-square] and most frequently reported side effects were between ages 8 and 10years. None had permanent defects. It was observed that 4.27% reported with severe malaria manifesting as convulsion, anemia, splenomegaly and hyperpyrexia. They were treated with quinine and artemether at 10mg\kg and 1.6mg\kg respectively. 2.33% had spinal meningitides and were treated with penicillins and cephalosporins. None was hospitalized as a result of side-effect. No death recorded during therapy. It was observed that 0.73% reported with severe malaria and they were treated with either quinine or artemether at 10mg\kg and 1.6mg\kg respectively. 2.27% had spinal meningitides and were treated with penicillin or cephalosporin class of antibiotic.

Table 1: Clinical Parameters

Number of Patients	1500
Age [Years]	4.8±3.14years
Weight [Kg]	21±4.12kg
Temperature [^{0}C]	38.29±1.03 °C
Parasite Count	13,060± 6.09 number of parasite per microlitre

Clinical parameters of the randomly selected patients that were administered Artemether-Lumefantrine

Table 2: FREQUENCY OF SIDE-EFFECTS REPORTED

SIDE-EFFECTS AMONG AGE				DIZZINESS	FEVER	INSOMNIA	BODY WEAKNESS	ITCHING	BLURRED VISION	INCREASE HEART BEAT	STOMACH UPSET	HEADACHE	CONFUSIONANXIETY	DIARRHOEA	LOSS APPETITE	CONVULSION	CHANGE IN URINE COLOR	EAR PAIN
AGE YEARS	N	YES	NO															
2-4 [%]	617 [41.1]	561 [37.40]	56 [3.73]	368	126	72	276	-	-	67	-	-	1	21	31	4	31	-
5-7 [%]	482 [32.1]	443 [29.53]	39 [2.60]	391	67	61	337	1	64	16	1	10	2	2	54	1	26	3
8-10 [%]	401 [26.7]	395 [26.33]	6 [0.40]	214	114	48	392	3	121	24	2	72	31	5	11	-	54	1
N [%]	**1500**	**1399 [93.27]**	**101 [6.73]**	**973 [31.00]**	**307 [9.00]**	**181 [5.00]**	**1005 [32.00]**	**4 [0.13]**	**185 [5.92]**	**107 [3.42]**	**3 [0.10]**	**82 [2.62]**	**34 [1.09]**	**28 [0.9 0]**	**96 [3.07]**	**5 [0.16]**	**111 [3.55]**	**4 [0.123]**

Side-effects reported were dependent on the ages of patients [$p<0.05$ Chi-square]

DISCUSSION

Out of the randomly selected patients, it was observed that higher percentage reported with body weakness as the commonest side-effects. This can be attributed to one of the symptoms of uncomplicated malaria. Children may have shown this due to withdrawal from previous daily activities such as school and regular plays. It is difficult to assess safety of drugs in children particularly of younger age because of the challenging pharmacokinetic disposition that may have been influenced by the ongoing development of organs [7]. Convulsion as shown in this study could be related to the progression into severe malaria. It is a common practice among parents and guardians in the environment to delay unnecessarily before seeking medical attention. They may have utilized concoctions/decoctions of *Azadirachta indica, Carica papaya, Momordica charantia, Parguetina nigrescence* as alternatives in the treatment of malaria as reported by some authors [8]. Their utilization prior to report at the clinic could have influenced therapeutic and safety profiles of the Artemether-Lumefantrine. Home-based approach using combination therapies may be more ideal in preventing uncomplicated malaria rather than plants extract. Meanwhile, home-based treatment is already being recommended in many endemic areas like ours due to lack of access to health facilities [9]. The effects of other therapies such as paracetamol, multivitamins and other iron containing drugs cannot be excluded. Their utilization may have served their primary roles as antipyretic, immune boosters and iron supplement respectively. Diet most especially fat containing meals have been documented to influence the therapeutic and toxicological potentials of Lumefantrine [dichlorobenzylidine] and Halofantrine [9-phenanthrenemethanol] containing drugs [10, 11]. Cardiac effects as in QTc interval prolongation and arrhythmias have been known to be associated with the use of the Halofantrine.

Lumefantrine lacks the cardiac effects of Halofantrine [12-15]. The report of increased heart beat in this study could be related to the Lumefantrine component, despite the lower degree of QTc interval prolongation associated with it in children and adults compared to chloroquine, mefloquine, and halofantrine [10]. The overall effect of diet seems to be difficult to distinguish because many of the participant were of poor socio-economic status, they may not have found it difficult to avoid fatty food even when their parents were advised to avoid them. Pruritic side-effect was rare in this study. This may be similar to earlier episodes of pruritic rash in a study in Thailand [12].

Toxicities that have been frequently reported in several literatures may be difficult to assess in children most especially in areas such as ours where facilities are lacking. Children will generally find it difficult to express their experiences except in instances when the side-effects as reported in the survey were very severe. In this study, higher proportion of children above five year reported with more frequent side effects. This can be attributed to their being able to express how they felt during and after therapy. However it was observed that side effects reported were dependent on age of the patients,[$p<0.05$ Chi-square]. Results from this kind of study can be very useful to predict drug safety in pregnancy.

In the last two decades, artemisinin and its semi-synthetic derivates artemether and artesunate have been established as safe and effective antimalarials [16-18]. The toxicity of the artemisinin drugs is much lower than that of quinine, or even that of chloroquine. Significant adverse effects or signs of toxicity have not been reported in human patients treated with therapeutic dosages [16]. Some authors have reported that Artemisinin and its derivatives appear to be generally well tolerated; there have been reports of mild gastrointestinal disturbance (including nausea, vomiting, diarrhea, and abdominal pain), dizziness, headache, tinnitus, neutropenia, elevated liver enzyme values, and ECG abnormalities including prolongation of the QT interval [19]. All these reports may be common among adults, extending such profiles to pregnant women and children as most afflicted [5] can be useful in reducing the burden of malaria. The overall effect can be worse if they are combined with other antimalarials which they have potential additive/synergistic effect. Meanwhile, it is interesting to recall that the rationale for drug combinations is to improve treatment cure rate, and delay the emergence of drug resistance [3]. Such combinations can lead to fatalities most especially when such agents have similar pharmacodynamic fate.

Subjecting children to new drugs may be too risky. Rather than waiting for the full manifestation of malaria which will certainly degenerate to severe malaria if not promptly treated. Due to the burden of malaria in this region, patients may have been prone to re-infection thereby necessitating the use of Polymerase Chain Reaction [PCR] techniques to distinguish the possibilities of new infection. Preventive measures such as the use of bed nets, insecticides, and possibly prophylactic drugs can reduce the risk of new infections and minimize the consequences of new drugs. Other safety evaluation such as frequent withdrawal of blood samples would have been a useful parameter in assessing hematological safety, few parents\guardians wished to go through such rigorous investigation. Instead they prefer mere observation through facial expression and routine urine samples which will not reflect objective findings.

The gastrointestinal upset reported may be related to the direct irritant effect of the drug on the mucosa or indirect effect on the cytoprotective mechanism of prostaglandin E2 or alteration of cholinergic functions. As a limitation to this study, reports of side-effect may not have shown in the three day therapy [Acute toxicity] there may be other possible side-effects on a long time use [Chronic toxicity]. The following adverse effect have been reported with lumefantrine in combination with artemether commonly include headache, dizziness, sleep disturbance, palpitations, gastrointestinal disturbances, anorexia, pruritus, rash, cough, arthralgia, myalgia, and fatigue. The safety of Artemether-lumefantrine has been extensively reviewed in several trials [20]. In Africa, efficacies have been demonstrated in children [21-28]**.** Re-admission of some children reporting with fever, convulsion and anemia may not be related to the side-effects of the drugs but due to degeneration to severe malaria. Immunity could thus offer some degrees of protection for those that did not report [29, 30]. Central nervous system side-effects such as headache, dizziness, insomnia, blurred vision and loss of appetite could also be related to the primary symptoms of uncomplicated malaria. Although majority of the children that came for these free drugs were mal-nourished because of parents' low socio-economic status; the overall effects of food and nutrition cannot be excluded as influential factors. Spinal meningitides that necessitated the use of penicillins and cephalosporins could be as a result of poor hygiene and nutrition as commonly observed among children in the region.

Auditory side effects, although few in this study, there are evidences of a significant and irreversible loss in hearing [31]. And animal toxicological studies with the artemisinin derivatives have been the development of an unusual selective pattern of neuronal damage to certain brainstem nuclei, particularly also involved in hearing and balance [32, 33]. The increased hearing threshold seems to be related to age and not sex. This finding may be related to environmental or genetic factors and unrelated to previous exposure to Artemether-Lumefantrine. To further explain this, few cases of ear pain as observed in the study, are not too significant to draw a general conclusion on the effect of the combination in the auditory system. However, there are evidences of audiometric studies that were conducted on pre-exposure baseline measurements [34-37].

CONCLUSION

It was quite clear that Artemether-Lumefantrine was safe among children below ten years. The study recommends that children below two years such as infants and neonates should be investigated in order to extend safety impression among the groups afflicted with malaria. The rational utilization of Arthemether-Lumefantrine will lead to a significant reduction in the morbidity and mortality of malaria in the afflicted group as previously documented in African regions [38, 39].

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