

Tolerabilities of Artemisinin-Based Combination Drugs among Patients with Uncomplicated Malaria in a Tertiary Institution Benin City, Nigeria

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Abstract

Background: The policy governing the treatment of malaria in Nigeria was changed in 2005 instituting the Artemisinin-Based Combination Therapies [ACTs] as first-line Drugs instead of Chloroquine due to rapidly developing resistance of *Plasmodium falciparum*.

Methodology: The tolerability to [ACTs] was assessed in patients using a structured questionnaire and Visual analogue scale. These instruments were distributed systematically among the patients that presented with uncomplicated malaria after obtaining consent from the University of Benin Teaching Hospital, Benin City, Nigeria.

Results: Among the five hundred and twenty patients that participated in the tolerability assessment of four different types of ACTs, male and female ratio was 1.3:1, Mean age 32.06 ± 2.3 years [Mean ± SD]. Artemether-Lumefantrine was the most frequently utilized and most tolerable. Two hundred and five [52.69%] respondents reported with forty-one different types of adverse effects of nine major systemic classes. Body weakness was the most frequent adverse effects reported in 112[54.63%] respondents. Adverse effects were significantly dependent on the type of ACTs used $p < 0.05$; these were found to be most common with Artesunate-Mefloquine. Eleven patients were hospitalized due to very severe Body weakness and Dizziness. These severities were found common with Artesunate-Amodiaquine and Artesunate-Mefloquine respectively. Despite the adverse effects, four hundred and seventy-six respondents (91.53%) were willing to repeat ACTs another time they have malaria. There were significant differences in symptomatic response on Days 0, 1, 2, 3, 7, 14 and 28 ($p < 0.05$). 93% respondents felt extremely sick on Day 0, 68% had persistent fever on the third day of treatment and 71% had improved response after day 7.

Conclusion: Anecdotal reports showed that ACTs have a modest tolerability, they are therefore recommended for patients that have uncomplicated malaria.

Keywords: Tolerability; Adverse effects; ACTs; Malaria; Policy

Introduction

In recent years new drug therapies were introduced in the treatment of major tropical diseases. Since large populations are often involved on repetitive exposure as in case of malaria, there is need for close monitoring of possible adverse reactions as suggested [1].

The antimalarial programs in the sub-Saharan African countries are recent examples of public health initiatives where safety has been a priority. Due to the frequent report of resistance to many monotherapeutic antimalarials, up to 106 countries have adopted Artemisinin-Based Combination Therapies as first-line agents for the treatment of uncomplicated malaria [2]. This treatment policy was adopted by the Federal ministry of health Abuja- Nigeria in the year 2005. Following this, many clinicians have imbibed the prescription of ACTs in the treatment of uncomplicated malaria within the country. The major drawback of these new therapies in our environment is the cost. This has been estimated to be ten times more expensive than monotherapies [3].

Although combination therapies are accepted as the rational approach in malaria management in Africa, current evidence of their effectiveness within the African region is limited. There is little or no information on the safety and efficacy of combination treatment in a large populace most especially the high-risk group such as pregnant woman and children [2]. The use of drugs in therapy irrespective of the drugs choice and disease condition can result in tolerable side-effects, and intolerable adverse effects among patients [4].

The scope of this work is to assess the tolerability among individuals that reported with uncomplicated malaria and to validate whether

malaria symptoms were potentiated or resolved by Artemisinin-Based Combination Therapies in the University of Benin Teaching Hospital, Benin City Nigeria.

Materials and Methods

Before the study was carried out the approval was sought and obtained from the Ethical committee in the University of Benin City Teaching Hospital Benin City, Nigeria. Sample size calculated using an adapted formula [5]. Five hundred and twenty patients that met the inclusion criteria were randomly selected and administered a three page structured questionnaire adapted from past authors [4]. Methods of administration were by self-administration and face-face interview for literates and non-literates respectively. The procedures for filling were explained to the participants prior to the exercise. ACTs assessed for tolerability were Artesunate-Lumefantrine, Artesunate-Amodiaquine, Artesunate-mefloquine and Artesunate- Sulfamethoxy-pyrazine-Pyrimethemine. Duration of study was between January and December

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2008. Patients recruited for the study were those that presented with features of uncomplicated malaria such as fever, headache, chills or rigors, general weakness, vomiting, loss of appetite and profuse sweating. They were prescribed ACTs. Patients that withdrew their consent, unable to report back, presenting with intolerable side/adverse effects necessitating hospitalization, emergence of concomitant disease, degeneration to severe malaria, utilization of antimalarials or antibiotics with antimalarial outside the ACTs prescribed and inappropriately filled questionnaire were not included in the study.

Visual analogue scale measures developed by previous authors [6] were modified and used as instruments to assess the responses to Artemisinin-Based Combination Drugs. This evaluated whether malaria symptoms were potentiated or resolved during utilization. Meanwhile, two hundred patients that met the inclusion criteria were administered the Visual Analogue Scale measures. All measures were administered by face-to-face interviews to ensure adequate reporting. Respondents were expected to indicate their responses to therapy by marking a perpendicular line the between 0mm and 100mm scale. The scale between 0mm and 100mm scale with extreme adjectives represents a measure between “*extremely well and extremely sick*”; “*extremely calm and extremely restless*”; “*extremely strong and extremely weak*”. These Visual analogue scale measures were administered on Days 0, 1, 2, 3, 7, 14, and 28 of the study.

Statistical methods

Data generated were grouped as respondents characteristics, types of ACTs used, antimalarials used before policy and pattern of adverse effect reported. Data were entered into Microsoft excel SPSS version 11.0 (SPSS, Inc. Chicago, IL) Where necessary, they were computed as percentages, mean \pm SD. Non-parametric data were assessed for significance using Chi-square, parametric data were assessed using student t-test and analysis of variance. p-values less than 0.05 were regarded as significant.

Results

Among the five hundred and twenty patients that participated in the tolerability assessment of four different types of ACTs, male and female ratio was 1.3:1, Mean age 32.06 ± 2.3 years [Mean \pm SD]. Artemether-Lumefantrine was the most frequently utilized and most tolerable. Two hundred and five [52.69%] respondents reported with forty-one different types of adverse effects of nine major systemic classes as in Table 1. Body weakness was the most frequent adverse effects reported in 112[54.63%] respondents. Adverse effects were significantly dependent

on the type of ACTs used $p < 0.05$; these were found to be most common with Artesunate-Mefloquine. Eleven patients were hospitalized due to very severe Body weakness and Dizziness. These severities were found common with Artesunate-Amodiaquine and Artesunate-Mefloquine respectively. Despite the adverse effects, four hundred and seventy-six respondents (91.53%) were willing to repeat ACTs another time they have malaria. There were significant differences in symptomatic response on Days 0, 1, 2, 3, 7, 14 and 28 ($p < 0.05$). 93% respondents felt extremely sick on Day 0, 68% had persistent fever on the third day of treatment and 71% had improved response after day 7.

The number of respondents that used individual ACTs was Artemether-Lumefantrine 250 (48.08%), Artesunate-Amodiaquine 106(21.00%), Artesunate-Mefloquine 145(28.0%), Artesunate-Sulphamethoxy-pyrazine-Pyrimethamine 19(3.65%). They reported with adverse-effects as Artemether-Lumefantrine 79(31.60%), Artesunate-Amodiaquine 88(83.01%), Artesunate-Mefloquine 102(70.34%) and Artesunate-Sulphamethoxy-pyrazine-Pyrimethamine 16(84.21%) as in Figure 1. Malaria symptoms were resolved significantly resolved rather than being potentiated during the period of investigation as in Figure 2.

Discussion

The study showed that Artemether-Lumefantrine was the most tolerable being that least proportion of respondents presented with adverse effects after its use. This may be related to suiTable doses that will not cause harm. This is similar to findings previous studies [7-12].

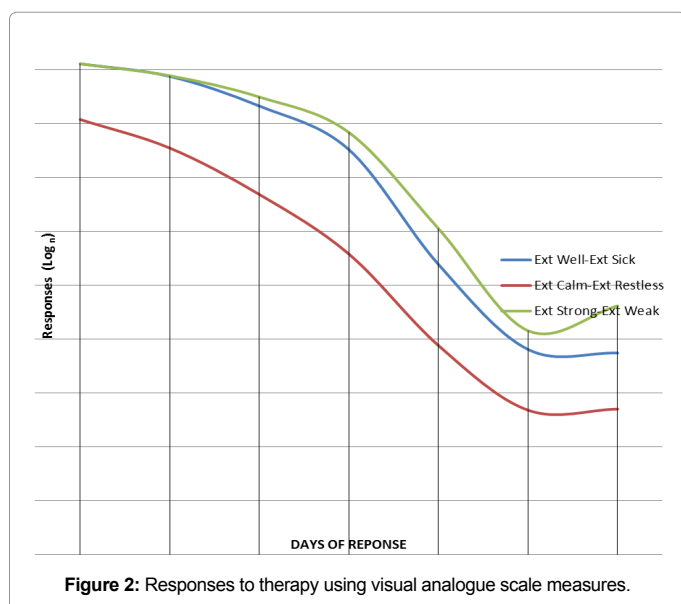
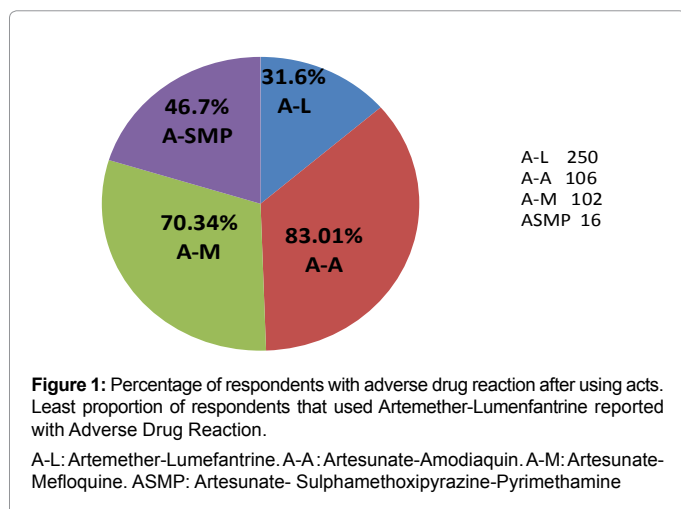
Other combinations utilized that have shown intolerabilities could be due to high doses in the combinations. Artemisinin derivatives component may have acted in synergy with the other drugs, thus potentiated the reported adverse effects. These adverse effects seem similar to those reported in animal and human subjects when used singly [13]. It is interesting to note that when new agents are introduced into therapy, it does not necessarily mean they are safe even when such have been certified at preliminary phases. There may be need for withdrawal most especially when there are reports of toxicities at post-marketing stage.

As seen in this study, few cases of intolerabilities that resulted in hospitalization of affected patients suggest retaining of ACTs for malarial therapy in the environment. The intolerabilities were found to be more common with Artesunate-Mefloquine and Artesunate-Amodiaquine presenting as body weakness and dizziness respectively. All these serious adverse effects were managed by the physicians symptomatically and patients were discharged home within one day.

Organ Class	Freq 1116	Most Freq Type Of Adr	A-L 379[33.96]	A-A 343[30.74]	A-M 380[34.05]	A-SMP 14[1.26]
GIT	243[21.77]	SUP [8.15]	78[32.10]	79[32.51]	86[35.39]	-
MUS	216[19.36]	BW[16.04]	74[34.26]	52[24.07]	88[40.74]	2[0.93]
CNS	389[34.87]	DIZZ[11.64]	123[31.62]	130[33.42]	130[33.42]	6[1.54]
SKIN	68[6.09]	SW [3.40]	23[33.82]	25[36.77]	18[26.47]	2[2.94]
OCU	107[9.59]	BV [8.69]	29[27.10]	25[23.37]	51[47.66]	2[1.87]
RENAL	46[4.12]	CUC [3.32]	29[63.04]	15[32.61]	2[4.35]	-
CVS	29[2.60]	IHR [2.06]	17[58.62]	8[27.59]	4[13.79]	-
RESP	16[1.43]	DB [0.81]	6[37.5]	7[43.75]	1[6.25]	2[12.5]
AUD	2[0.18]	EP [0.18]	-	2[0.18]	-	-

CNS: Central Nervous System; OCU: Ocular; CVS: Cardiovascular System; AUD: Auditory; EP: Ear pain; DB: Difficulty in breathing; IHR: Increased Heart Rate; CUC: Changes in Urine Color; BV: Blurred Vision; SW: Sweating; DIZZ: Dizziness; BW: Body weakness; SUP: Stomach Upset; ADR: Adverse Drug Reaction; A-L: Artemether-Lumefantrine; A-A: Artesunate-Amodiaquin; A-M: Artesunate-Mefloquine; ASMP: Artesunate- Sulphamethoxy-pyrazine-Pyrimethamine; Freq: Frequency. MUS: Musculoskeletal; Adverse-effects reported were dependent on ACTs used. $P < 0.05$ [chi-square]

Table 1: Percentage frequencies of common adverse effects reported after using acts.



This aspect further suggests that the doses in these combinations should be adjusted in order to improve their tolerance.

Serious adverse effects leading to prolongation of hospital stay or deaths not reported in this study could be attributed to the remarkable level of tolerance to ACTs. This can be attributed to the artemisinin derivative components that are known to have wide therapeutic index [13,14]. Although in animals such as rats, dogs, and monkeys, artemether, the methyl ether derivative of artemisinin, has been reported to be associated with an unusual toxicity pattern in specific brain nuclei involving the auditory and vestibular pathways [15,16]. This has not been observed in humans and studies using auditory brainstem responses in patients exposed to artemisinin derivatives [17,18].

Previous studies on tolerability of ACTs have been reports of a meta-analyses pooled from twenty-six different randomized studies of sample size n=10,266 in different regions [19]. In the series, two or three ACTs were assessed and few cases were reported in Nigeria. Among the few cases as reported [20], tolerability studies of Artemether-lumefantrine were reported among few children below ten years in the use of in Benin City. All these had some limitations. Interestingly, this

study therefore reports some adverse effects after assessing four ACTs among different age groups.

Gastrointestinal upsets that were found to be common with Artesunate-Mefloquine followed by Artesunate-Amodiaquin; this may be related to the direct irritant effect of the drug on mucosal wall, indirect influence on the cytoprotective mechanism of prostaglandin E₂ or alteration of the cholinergic function as observed [21]. The study therefore suggests ACTs should be taken after meals to reduce the gastrointestinal effects. Anxiety/confusion that was commonly noted with Artesunate-mefloquine may be due to mefloquine in the combination. This could be related to the neuropsychiatric effect that is common with mefloquine as reported previously [22]. Cardiac adverse-effect that was more common with Artemether-Lumefantrine may be related to Lumefantrine component which is similar to Halofantrine in the prolongation of QTc interval as previously reported [22]. Similar cardiac adverse-effects have been reported with other antimalarials, such as quinine, quinidine, in the prolongation of the QTc interval at therapeutic doses [11,23]. They attributed this effect to the aryl alcohol analogue common in their structures. Patients reporting with body weakness, blurred vision and dizziness as found to be most frequently linked with Artesunate-Mefloquine. Sweating as seen common with Artemether-Lumefantrine may reflect symptomatic relief rather than adverse-effect of the drug. Adverse-effects reported may be related to the primary symptoms of uncomplicated malaria before the onset of therapy as observed by some previous authors [24]. It is worthy to note that malarial symptoms were not potentiated rather they were resolved gradually by ACTs despite the reported adverse-effects seen in early days of initiating therapy.

All the adverse-effects were found to be dependent on the type of ACTs utilized by the patient (p<0.05 Chi-square), their significant differences can be attributed to the varied adverse effects that may be peculiar to the individual drugs in the combination. Patients claiming that they would never take ACTs another time they had malaria may be related to the severity of adverse-effects experienced. Higher proportion willing to repeat the drugs may be related to subjective response to efficacy. As a follow up to this study, it is desirable to carry out efficacy study to ascertain the claim by past workers [25]. Patients reported that they had been using chloroquine and sulphadoxine-pyrimethamine as most common monotherapeutic antimalarials before the adoption of the new policy, may be related to the cost and availability of the agents [3]. Report of pruritus, though rare with Artesunate – mefloquine and Artesunate-amodiaquine as in this study, this may be related to the quinoline analogue that is in chloroquine [26,27]. In Nigeria, reports of chloroquine, pyrimethamine-sulfadoxine failures have been documented [28]. Higher proportion of patients withdrawing from their use may be related to their side-effects and poor efficacy associated with the drugs.

Reports of adverse-effects as seen in this study showed a pattern of acute toxicities during the period of therapy. There may be other possible adverse-effects that are inherent among these agents during repeated/long term use. The study therefore suggests more exploratory studies involving sampling of biological fluid to know the effect on the major organs.

Conclusion

ACTs were found to be tolerable among most patients. Therefore ACTs are recommended for the treatment of uncomplicated malaria.

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