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A SURVEY OF THE RATIONAL USE OF ARTEMISININ-BASED COMBINATION THERAPIES (ACTs) FOR THE TREATMENT OF MALARIA AMONG HEALTH PRACTITIONERS IN OGUN STATE, SOUTH WEST NIGERIA

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ABSTRACT
This study was carried out in health institutions in Ogun State to evaluate the rational use of artemisinin based combination therapies (ACTs) for the treatment of malaria. Data was collected using structured questionnaires. A total of 200 questionnaires were administered and returned. One hundred and eight (108) (54%) doctors and 92 (46%) pharmacists were interviewed. Eighty six (86) (79.6%) doctors and 82 (89.1%) pharmacists agreed that the ACTs were more effective than monotherapy for the treatment of malaria. Twenty (20) (18.5%) doctors still thought that monotherapy was more effective and 2 (1.9%) doctors were indifferent. Forty nine (49) (45.4%) doctors and 70 (76.1%) pharmacists use ACTs as first line antimalarial. Out of the 200 respondents, 173 (86.5%) were not aware that taking antioxidants such as vitamin C concurrently with the ACTs caused an inhibition of antimalarial effect. One hundred and sixty two (162) (81%) of total respondents took precautions while administering the ACTs and 38 (19%) took no precautions such as: "avoid alcohol and cigarettes" (83.5%), "take with fatty meals" (98.5%), "report any side effect immediately" (63.5%) and "don't combine with any drug or herbal mixture for the first 24 hours" (12.5%). Ninety two (92) (85.2%) doctors and 72 (78.3%) pharmacists always order for a laboratory investigation before prescribing the ACTs. Twenty two (22) (20.4%) doctors and 12 (13.0%) pharmacists monitor patient's compliance with medication by getting feedback from the patients. Fifty five (55) (53.9%) doctors and 82 (89.1%) pharmacists never documented adverse effect of ACTs experienced by the patients. ACTs were prescribed by 100% of the respondents in the second and third trimester of pregnancy because of their safety during these periods of pregnancy. Using statistical package for social sciences (SPSS), awareness that the ACTs taken with antioxidants such as ascorbic acid, antimalarial effect increases with practitioners' years of practice. Most of the practitioners' stocks of ACTs are from medical representatives, therefore pharmaceutical companies will play a pivotal role in providing these drug information in literatures distributed to the health practitioners with comprehensive information on the proper use of the ACTs.

Keywords: pharmacists, doctors, artemisinin, malaria, rational use, combination therapy

INTRODUCTION

Malaria is characterized by chills, fever, anaemia, splenomegaly and damage to organs such as the liver and brain. It could be an acute or chronic mosquito-borne disease in man. Malaria is caused by the presence of a unicellular parasite, a protozoan, belonging to the genus Plasmodium in the red blood corpuscles and in the liver cells of man. The protozoan is transmitted to man by the bite of injected female

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mosquitoes of the genus Anopheles. It can also be transmitted congenitally via the placenta of an infected mother, or following blood transfusion from a donor with malaria

According to the World Health Organization (WHO 2003) report, 56% of the world population live in the endemic regions. Over 80% of the world's cases of malaria occur in Africa with the disease being highly stable in West Africa with peak transmission during the rainy season. Nigeria is holoendemic for malaria with a high stability index. Recent estimates of the global burden have shown increasing levels of malaria morbidity and mortality, reflecting the deterioration of the malaria situation in Africa during the 1990s. About 80% of all malaria deaths occur in Africa, south of the Sahara, and the great majority of them in children under age of five (WHO, 2005a).

Key among the factors contributing to the increasing malaria mortality and morbidity is the widespread resistance of *Plasmodium falciparum* to conventional anti malarial drugs, such as chloroquine, sulphadoxine-pyrimethamine (SP) and amodiaquine multidrug resistant. *P. falciparum* malaria is widely prevalent in South-East Asia and South America. To date, Africa, the continent with the highest burden of malaria, is also affected.

Resistance to inexpensive monotherapies such as chloroquine and SP has developed or is developing rapidly, with increased mortality as a result.

The inappropriate use of anti malarial drugs during the past century has contributed to the current situation whereby anti malarial drugs are deployed on a large scale, always as monotherapies or introduced in sequence, and were generally poorly managed in that their use was continued despite unacceptably high level of resistance. Over the past decade, a new group of antimalarials-the artemisinin compounds, especially artesunate, artemether and dihydroartemisinin, have been introduced on an increasingly large scale. These compounds produce a very rapid therapeutic response such as reduction of the parasite biomass and resolution of symptoms. They are active against multidrug resistant and are well tolerated *P. falciparum* by the patients and reduce gametocyte carriage. Thus they have the potential to reduce transmission of malaria. To date, no resistance to artemisinin or artemisinin derivatives has been reported, although some decrease in sensitivity *in vitro* has been detected in China and Viet Nam (WHO, 2005b). If used alone, the artemisinins will cure *P.falciparum* malaria in 5 days, but studies have shown that in combination with certain synthetic drugs, they produce high cure rates in 3days with higher adherence to treatment (WHO, 2005b).

This study sought to assess the knowledge of doctors and pharmacists in the rational use of the artemisinin-based combination therapies (ACTs) with regard to their use with antioxidants, methods of monitoring compliance, patient counselling and therapeutic drug monitoring with the goal of providing and promoting pharmaceutical care.

MATERIALS AND METHODS

The study was carried out in selected healthcare facilities in Ogun State. The health facilities were private clinics, government hospitals and community pharmacies. The target population in the area of study included practicing pharmacists and doctors in health care facilities in Ogun State in South West Nigeria. 200 questionnaires were administered to

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200 health practitioners and they were selected by simple sampling. A total of 108 doctors and 92 pharmacists were interviewed.

The information was collected with the use of well structured questionnaires to gather information on precautions taken before ACT administration, method of monitoring of compliance, request for laboratory investigation before prescribing the ACTs and factors that contribute to the rational use of the ACTs.

RESULTS

One hundred and eight (108) (54%) doctors and 92 (46%) pharmacists were interviewed. Of the total respondents, 86 (79.6%) doctors and 82 (89.1%) pharmacists agreed that the ACTs were more effective than monotherapy for the treatment of malaria, Twenty (20) (18.5%) doctors still thought that monotherapy was more effective
and 2 (1.9%) doctors were indifferent. Forty nine (49) (45.4%) doctors and 70 (76.1%) pharmacists used the ACTs as first line antimalarial. One hundred and seventy three (173) (86.5%) of the 200 respondents were not aware that taking antioxidants such as vitamin C concurrently with the ACTs caused an inhibition of antimalarial effect. One hundred and sixty two (162) (81%) of total respondents took precautions while administering the ACTs and 38 (195) took no precautions such as: avoid alcohol and cigarettes,(83.5%), take with fatty meals (98.5%), report any side effect immediately(63.5%), do not combine with any drug or herbal mixture for first 24 hours(12.5%). 92 (85.2%) doctors and 72 (78.3%) pharmacists always order for a laboratory investigation before prescribing the ACTs. Twenty two (22) (20.4%) doctors and 12 (13%) pharmacists monitored patient's compliance with medication by getting feedback from patients. Fifty- five (55) (53.9) doctors and 82 (89.1%) pharmacists never documented adverse effects of ACTs experienced by the patients. In the second and third trimester of pregnancy, 100% of respondents prescribed the ACTs. Statistical analysis was done using SPSS version 11.0 software programme for frequency distribution and cross tabulations.

DISCUSSION

The ACTs exhibit their pharmacological activity based on synergistic activity of two classes of antimalarials having different mode of action bringing about a better reduction of biomass of the *plasmodium* titer. This action results in better malarial control (WHO, 2001). Because of their different modes of action, likelihood of resistance development is reduced (Plowe, 2003).

The result from this study shows that the total numbers of 200 (100%) questionnaires administered were returned. This comprises of 108 (54%) doctors and 92 (46%) pharmacists. Eighty six (86) (79.6%) doctors and 82 (89.1%) pharmacists were aware that the ACTs were more effective than monotherapy for the treatment of malaria (White, 2002) (Table 1).

Some health practitioners still rely on some classes of monotherapies to treat malaria as most of such practitioners believe that chloroquine has better control than arteminsinin combination therapy (ACTs). (Bloland, 2000, White, 2002; Wellems, T. & Plowe, 2001). They argue that since chloroquine has been left alone for so long and focus has been on other classes of antimalarials, the time lapse without use of chloroquine must have reversed the resistance that formally developed with the use of chloroquine

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thereby making it highly effective when used now.

Table 1: Frequency distribution of respondents according to awareness that the ACTs are more effective than monotherapy, use of the ACTs as first line treatment of malaria and effects of antioxidants on the efficacy of the ACTs.

	DOCTORS			PHARMACISTS		
Awareness that the ACTs are more effective than monotherapy	Frequency	Percent	Cumulative Percent	Frequency	Percent	Cumulative Percent
Yes	86	79,6	79.6	82	89.1	89.1
No	20	18.5	98.1	10	10.9	100.0
No Answer	2	1.9	100.0	-	-	100.0
Total	108	100		92	100	
Use of the ACTs as first line treatment of malaria						
Yes	49	45.4	45.4	70	76.1	76.1
No	25	23.1	68.5	16	17.4	93.5
No Answer	34	31.5	100.0	6	6.5	100.0
Total	108	100		92	100	
Awareness effect of antioxidants on the efficacy of the ACTs						
Yes	16	14.8	14.8	11	11.9	11.9
No	92	85.2	100.0	81	88.1	100.0
Total	108	100.0			100.0	

Table 2: Frequency distribution of respondents according to precautions taken while administering the ACTs.

PRECAUTION	DOCTORS		PHARMACISTS	
	Frequency	Percent	Frequency	Percent
Avoid alcohol and cigarettes	89	82.4	78	84.8
Take with fatty meals	107	99.1	90	97.8
Report any side effects immediately	93	86.1	34	36.9
Take at regular times everyday	98	90.7	45	48.9
Don't take on empty stomach	82	75.9	14	15.2
Don't combine with any drug or herbal mixture for first 24 hours	23	21.3	2	2.2
Take with plenty of water	94	87.0	88	95.7
Do not miss any dose	12	11.1	22	23.9
Avoid antioxidants e.g., Vitamin C	9	8.3	2	2.2

Respondents could pick more than one option

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Table 3: Frequency of respondents based on respondents' order for a laboratory investigation before prescribing the ACTs

	DOCTORS			PHARMACISTS		
	Frequency	Percent	Cumulative Percent	Frequency	Percent	Cumulative Percent
Always	92	85.3	85.2	72	78.3	78.3
Sometimes	8	7.4	92.6	9	9.8	88.1
Never	8	7.4	100.0	11	11.9	100.0
Total	108	100.0		92	100.0	

Table 4: Frequency distribution of respondent according to documentation of adverse effects

Response	Doctors	Percent	Pharmacists	Percent
Always	10	9.3	3	3.3
Sometimes	2	1.8	3	3.3
Occasionally	30	27.8	4	4.3
Never	61	56.5	82	89.1
No Answer	5	4.6	0	0
Total	108	100.0	92	100.0

Table 5: Frequency distribution of respondents according to use of ACTs in pregnancy

Response	First trimester		Second trimester		Third trimester	
	Participants	Percentage	Participants	Percentage	Participants	Percentage
Use of ACT is safe	152	76.0	200	100.0	200	100.0
Use of ACT is not safe	48	24.0				
Total	200	100	200	100	200	100

Table 6: Tests of Statistics

Variables	Frequency	Mean	Standard deviation	Standard error of me
I know about the artemisinin-based combination therapies for treatment of malaria	168	1.2200	0.4388	0.0310
I agree that the ACTs are more effective than the monotherapy treatment of malaria to prevent resistance	184	1.3950	0.5750	0.4766
The ACTs are my firstline treatment of malaria no matter the severity	119	1.9450	0.8422	0.6305
Are you aware that the ACTs taken with ANTIOXIDANTS' such as found in fruits affecting anti-malarial effects?	27	1.9950	0.5536	0.3915
Do your patients comply with your prescriptions?	164	1.2400	0.5866	0.4150
You always order for a laboratory investigation before prescribing?	103	1.2400	0.5666	0.4148
How often do you empirically prescribe the ACTs?	200	1.8850	0.6511	0.4604
As a practicing health professional, are there any precautions you take before administering the ACTs?	200	1.2550.	0.4369	0.3090

Between Subject Factors

	Value Label	N
Are you aware that the ACTs taken with antioxidants such as found in fruits affects anti malarial effect	Yes	27
	No	173

Between Subject Factors

Dependent Variable: year of practice

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	57.332 (a)	2	28.666	17.754	.000
Intercept	1050.976	1	1050.976	650.897	.000
Aw	57.332	2	28.666	17.754	.000
Error	318.088	197	1.615		

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Total	2462.000	200			

Most health practitioners used the ACTs as first line drug of choice for all cases of malaria attack as 49 (45.4%) doctors and 70 (76.1%) pharmacists used the ACTs as first line treatment of malaria regardless of the severity of attack (Table 1)

Some of these practitioners use chloroquine or amodiaquine as monotherapy after which they add an artemisinin compound preferably intravenously. They argued that artemisinin has a poor antipyretic control thus necessitating the use of chloroquine or amodiaquine as monotherapies (White, 1997). Antioxidants effect on the efficacy of the ACTs was the awareness of the 16 (14.8%) doctors and 11 (11.9%) pharmacists (Table 1). Antioxidants are compounds found commonly in fruits, vitamin supplements and vegetables (Vertuani, 2004; Valko *et al.*, 2007). But a large number of respondents did not know about this fact. Antioxidants' effects on the efficacy of the ACTs can contribute immensely to cases of therapeutic failure encountered commonly with the ACTs (Shunmay and White, 2005).

Like any other drug, the ACTs should be used with precautions and the patients should be so educated. One hundred and seven (107) (99.1%) doctors and 90 (97.8%) pharmacists took a precaution of "Take with meal". Eighty nine (89) (82.4%) doctors and 78 (84.8%) pharmacists, 93 (86.9%) doctors and 34 (36.9%) pharmacists, 98 (90.7%) doctors and 45 (48.9%) pharmacists took precautions of "Avoid alcohol and cigarette", "Report any side effect immediately", "Take at regular times everyday" respectively while 82 (75.9%) doctors and 14 (15.2%) pharmacists, 94 (87.0%) doctors and 88 (95.7%) pharmacists were aware of patient education on precautions "Don't take on empty stomach", and "Take with plenty of water" respectively.

This indicates challenges on the part of the pharmacists who should really counsel patients when recommending ACTs to them, as majority of the pharmacists are unaware of the significant of precautions when administering ACTs to patients as has become obvious in this study, where only 2 (2.2%) pharmacists indicated awareness such as "Don't take on empty stomach" and "Avoid anti oxidants such as ascorbic acid (Vitamin C). (Table2)

Health practitioners especially the pharmacists should be able to effectively communicate the fact that artemisinin plus amodiaquine causes very severe weakness and dizziness. In any case of suspected malaria infection, a laboratory investigation should ideally be carried out first before prescribing the ACTs. Majority of the doctors, 92 (85.2%) and pharmacists, 72 (78.3%) believed that laboratory investigation should always be performed before ACTs are prescribed. Some health practitioners still prefer to prescribe and treat the malaria empirically. They argue that any fever suspected to be malaria and not bacterial is believed to be malaria, and since we live in a malaria endemic region it is better to first treat all fevers as malaria fever before ordering for a laboratory test (WHO, 2005c). In this study 8 (7.4%) doctors, 9 (9.8%) pharmacists believed that laboratory investigation should sometimes be performed before ACTs were prescribed and 8 (7.4%) doctors, and 11 (11.9%) pharmacists, believed that it is not necessary to undertake laboratory investigation before ACTs were prescribed. (Table 3)

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Health practitioners must be encouraged and trained to document all side effects and adverse effects of the ACTs as with all drugs (Nebeker *et al.*, 2004). A good number of respondents defaulted in this regard. (Table 4)

Health institutions should train all medical staff on how to document these adverse effects and on the interventions taken to reverse and control them (WHO, 2002). In this study majority of the respondents 61 (56.5%) doctors, and 82 (81.9%) pharmacists never documented adverse effects whenever ACTs were prescribed. Thirty (30) (27.8%) doctors and 4 (4.3%) pharmacists occasionally documented adverse effects. Ten (10) (9.3%) doctors, and 3 (3.3%) pharmacists always documented adverse effects with 2(1.8%) doctors and 3 (3.3%) pharmacists sometimes documented adverse effects, and 5(4.6%) doctors, none pharmacists gave no answer to the adverse effects documentation whenever ACTs were prescribed (Table 4).

The ACTs are a class of very safe drugs and can be used in all trimesters of pregnancy, but more preferably in the second and third trimesters of pregnancy (Quigui *et al.*, 2008; Rana *et al.*, 2007; Rogerson and Menendez, 2006). All the respondents, 200 (100%) doctors and pharmacists, were aware of this fact but only 152 (76.0%) of both doctors and pharmacists were aware of ACTs safety during the first trimester of pregnancy while 48 (24.0%) of respondents believed that ACTs were not safe during the first trimester of pregnancy (Table 5). Using statistical package for social sciences (SPSS) ($p<0.05$), awareness that the ACTs taken with antioxidants such as ascorbic acid, antimalarial effect increases with practitioners' years of practice (Table 6).

CONCLUSION

Trainings and seminars should be held at regular intervals to update medical practitioners on recent use and trends of prescribing and should also aim at enlightening them on the proper use of the ACTs. Pharmaceutical industries through their medical representatives have a major role to play in these trainings. All practicing pharmacists should ensure that proper advice, counselling and instructions that enhance compliance and rational use of the ACTs are given to the patients.

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