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EFFECT OF POLICY CHANGE ON THE PRESCRIPTION PATTERN OF ANTIMALARIAL DRUGS OF DOCTORS IN BENIN CITY.

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ABSTRACT

This study evaluates the prescriptions of antimalarial medicines before and after the change in the National Antimalarial Policy and ascertain the adherence of prescribers to the change in policy. It's a Retrospective and Descriptive study. The study was carried out in the out-patient department of the University of Benin Teaching Hospital and Central Hospital, both in Benin City, Nigeria. The study examined case records of adult patients ($\geq$ 18yrs) treated for uncomplicated malaria. One in every ten Case cards was sorted via Systematic Sampling.

Results showed that prior to the policy change, Artesunate monotherapy was the most prescribed antimalarial(37.3%), followed by Sulphadoxine-Pyrimethamine(SP) and Chloroquine(CQ) monotherapies,19.8% and 19.0% respectively. However three years into the change in policy, Artemether/Lumefantrine (AL) was the most prescribed, recording 25.2% as against 0.8% a year prior to the change in policy (2004).This was followed by Artesunate/Amodiaquine (AA) and Artesunate/Mefloquine (AM), 24.3% and 23.6% respectively. Artemisinin monotherapies and non-ACT combinations made up 10.3% and 5.1% of prescribed antimalarials in 2008 respectively. This study showed good adherence of prescribers to the change in antimalarial policy. This is encouraging, however there is need for stiffer regulations regarding Artemisinin monotherapies if success in malaria control must be achieved and the development of resistance prevented.

Introduction

Multidrug resistance plasmodium falciparum is a major public health challenge in malaria management especially in Sub-Saharan. Approximately 2.2billion people are affected by Plasmodium falciparum in 86 endemic countries, resulting in about 515million clinical cases worldwide yearly[1,2]. In Nigeria Plasmodium falciparum accounts for about 97% of all the malaria cases, and it is also the species most responsible for the severe form of the disease that leads to death in the country[3].

Since 1979 when chloroquine resistant plasmodium was first documented in East Africa, Plasmodium falciparum resistance has been documented for nearly all antimalarials currently available[4]. The changes in malaria management over the years are due mainly to the spread of multidrug resistant plasmodium falciparum. As a response to the increasing levels of antimalarial resistance, the World Health Organization (WHO) in 2001 recommended that countries experiencing resistance to conventional antimalarial monotherapies should switch to Artemisinin-based

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Combination therapies (ACTs) when managing uncomplicated malaria[5]. This was based on the high success rate that artesunate-mefloquine(AM) combination therapy recorded in South-East Asia, after years of high resistance to mefloquine monotherapy alone[6]. This change in policy was adopted by Federal Government of Nigeria in 2005 with Artemether-Lumenfantrine (AL) as the ACT of choice [7].The success of any treatment policy depends largely on the adherence of health care providers to treatment recommendations based on policy statements. Hence antimalarial prescriptions by prescribers are expected to be influenced by the change in the National antimalarial policy in other to improve the trend in malaria morbidity and mortality. The objective of this study was to evaluate the prescriptions of antimalarial medicines a year prior to and three years into the change of the National Antimalarial Policy (NAP) and ascertain the adherence of prescribers to the change in policy.

Methods

This retrospective and descriptive study was conducted in the General Outpatient Department of the University of Benin Teaching Hospital (UBTH) and the Central Hospital, Benin City, Southern Nigeria, between October 2009 and March 2010. The UBTH Out-patient clinic has an average daily turnout of about 400 patients. It serves the health facilities in the immediate five local government areas of Edo State and adjoining states of Delta, Kogi and Ondo. The Central Hospital is located in the heart of Benin City. It has a daily turnout of 350 patients. It is a referral centre for the Primary and secondary health care facilities within Edo state. Malaria is holo-endemic in this area with perennial transmission. Ethical clearance and administrative approval were obtained from the UBTH Ethics Committee and the Central Hospital Management respectively.

The case cards of adult patients ($\geq$ 18years) treated for uncomplicated malaria from 2004 to 2008 were identified. In drug use studies a minimum of 600 prescriptions are needed with a greater number if possible[8], thus one in every ten case cards was selected via systematic sampling. This yielded a total of 2,034 record cards. Relevant data extracted using a data collection form were patient's age, sex, method of confirmation of diagnosis and type of antimalarial prescribed. All data from the case record forms were coded accordingly and entered for statistical analysis using the Statistical Programme for Social Sciences (SPSS) software version 16.0. Results were expressed as means ($\pm$ standard deviation), percentages or median values where necessary. Descriptive statistics was used to summarize baseline values and demography. Z test was used to compare continuous variables. A P- value of < 0.05 was considered as statistically significant.

Results

A total of 2,034 patients' case files were evaluated during this study. The number of males were 761(37.4%) while 1,273(62.6%) were females. This gave a male to female ratio of 1:1.7. The mean age of the patients was 38.1$\pm$ 15.3years (range=18-94 years). Table 1 shows the age and sex distribution of patients.

Antimalarial Monotherapy Prescriptions

Prior to the change in the National Antimalarial Policy (NAP) in 2005, artesunate (AS) monotherapy was the

most prescribed antimalarial , accounting for 37.3% of all antimalarials in 2004. This was closely followed by Sulphadoxine/Pyrimethamine (SP) (19.8%) and Chloroquine (19%) respectively. Artesunate prescriptions fell sharply from 2005, and by 2008 dihydroartemisinin was the most prescribed of the antimalarial monotherapy (6.3%) (Table 2). Evaluation of percentage change in Antimalarial monotherapies prescribed between 2004 and 2008 (Table 3) showed that Artesunate (AS), Chloroquine (CQ) , Sulphadoxine-Pyrimethamine (SP) and Quinine (QN) prescriptions reduced significantly ($p<0.01$) three years into the change in the National Antimalarial Policy. However amodiaquine prescriptions significantly increased from 2004, although it accounted for 1% of all antimalarial prescriptions in 2008.

Antimalarial Combination Prescriptions

The trend of the ACTs from 2004 to 2008 is described in figure 1. Prior to change in policy the ACTs prescriptions were rare, with artemether-lumefantrine (AL) accounting for only 0.8% of the antimalarials prescribed. (Table 2)In 2005, there was a sharp rise in prescription of artesunate-mefloquine(AM) (40.4%) and by 2006 the ACTs were the most prescribed antimalarials, with artemether-lumefantrine (AL) exceeding artesunate-amodiaquine (AA) and artesunate-mefloquine (AM) prescriptions by 2007. (Table 2)There was a significant increase ($p<0.05$) in ACT prescriptions by 2008, AL (24.4%), AA (24.3%), and AM (23.6%). The antimalarial combinations prescribed other than the ACTs were combinations containing sulphadoxine/pyrimethamine(SP). Chloroquine/Sulphadoxine-Pyrimethamine combinations were the most prescribed among the non-ACTs in 2005(6.4%), this was however exceeded by Mefloquine/Sulphadoxine-Pyrimethamine prescriptions by 2006 (Table 2).

Table 1: **Age and Sex distribution of patients treated for malaria between 2004 and 2008.**

Age(years)	Male n (%)	Female n (%)	Total n (%)
≤ 20	59(36.8)	101(63.2)	160(100.0)
21 - 30	247(65.5)	430(34.5)	677(100.0)
31 - 40	175(38.2)	282(61.8)	457(100.0)
41 - 50	114(35.1)	210(64.9)	324(100.0)
51 - 60	92(41.3)	131(58.7)	223(100.0)
61 - 70	53(39.3)	82(60.7)	135(100.0)
71 - 80	20(44.4)	25(55.6)	45(100.0)
81 - 90	1(10.0)	9(90.0)	10(100.0)
91 - 100	0(0.0)	3(100.0)	3(100.0)
Total	**761(37.4)**	**1273(62.6)**	**2034(100.0)**

Table 2: Pattern of antimalarials prescribed before and after change of National Antimalarial Policy.

	Antimalarial	2004 (%)	2005 (%)	2006 (%)	2007 (%)	2008 (%)
Monotherapy	Chloroquine	388(19.0)	145(7.1)	170(8.3)	53(2.6)	47(2.3)
	Sulphadoxine-Pyrimethamine	401(19.8)	376(18.4)	229(11.2)	151(7.4)	112(5.5)
	Amodiaquine	0(0.0)	29(1.4)	16(0.8)	23(1.1)	20(1.0)
	Quinine	354(17.5)	102(5.0)	25(1.2)	43(2.1)	31(1.5)
	Halofantrine	0(9.0)	14(0.7)	2(0.1)	0(0.0)	0(0.0)
	Artesunate	762(37.3)	729(3.5)	94(4.6)	96(4.7)	65(3.2)
	Artemether	0(0.0)	0(0.0)	16(0.8)	23(1.1)	16(0.8)
	Dihydroartemisinin	113(5.6)	102(5.0)	157(7.7)	96(4.7)	129(6.3)
Artemisinin-based Combination Therapy	Artesunate/Amodiaquine	0(0.0)	0(0.0)	400(19.6)	284(13.9)	496(24.3)
	Artemether/Lumefantrine	16(0.8)	174(8.5)	157(7.7)	790(38.7)	515(25.2)
	Artesunate/Mefloquine	0(0.0)	821(40.4)	437(21.4)	349(17.1)	482(23.6)
	Chloroquine/SP	0(0.0)	131(6.4)	65(3.2)	0(0.0)	12(0.6)
	Amodiaquine/SP	0(0.0)	0(0.0)	10(0.5)	6(0.3)	0(0.0)
	Mefloquine/SP	0(0.0)	0(0.0)	88(4.3)	33(1.6)	84(4.1)
	Quinine/SP	0(0.0)	0(0.0)	0(0.0)	0(0.0)	8(0.4)
	Artesunate/Amodiaquine/SP	0(0.0)	0(0.0)	6(0.3)	0(0.0)	0(0.0)

SP- Sulphadoxine-Pyrimethamine

Table 3: Percentage change in antimalarials prescribed between 2004 and 2008.

ANTIMALARIAL DRUGS	2004 n(%)	2008 n(%)	%Change	Z	p value
Chloroquine	388(19.0)	47(2.3)	-16.7	17.25	0.00
Sulphadoxine-Pyrimethamine	401(19.8)	112(5.5)	-14.3	13.70	0.00
Amodiaquine	0(0.0)	20(1.0)	1.0	4.31	0.00
Quinine	354(17.5)	31(1.5)	-16.0	17.38	0.00
Artesunate	762(37.3)	65(3.2)	-34.3	27.07	0.00
Artemether	0(0.0)	16(0.8)	0.8	3.80	0.00
Dihydroartemisinin	113(5.6)	129(6.3)	0.7	0.88	0.38
Artesunate/Amodiaquine	0(0.0)	496(24.3)	24.3	23.72	0.00
Artemether/Lumefantrine	16(0.8)	515(25.2)	24.4	23.14	0.00
Artesunate/Mefloquine	0(0.0)	482(23.6)	23.6	23.33	0.00
Chloroquine/Sulphadoxine-Pyrimethamine	0(0.0)	12(0.6)	0.6	3.22	0.001
Mefloquine/Sulphadoxine-Pyrimethamine	0(0.0)	84(4.1)	4.1	9.13	0.00
Quinine/Sulphadoxine-Pyrimethamine	0(0.0)	8(0.4)	0.4	2.51	0.012

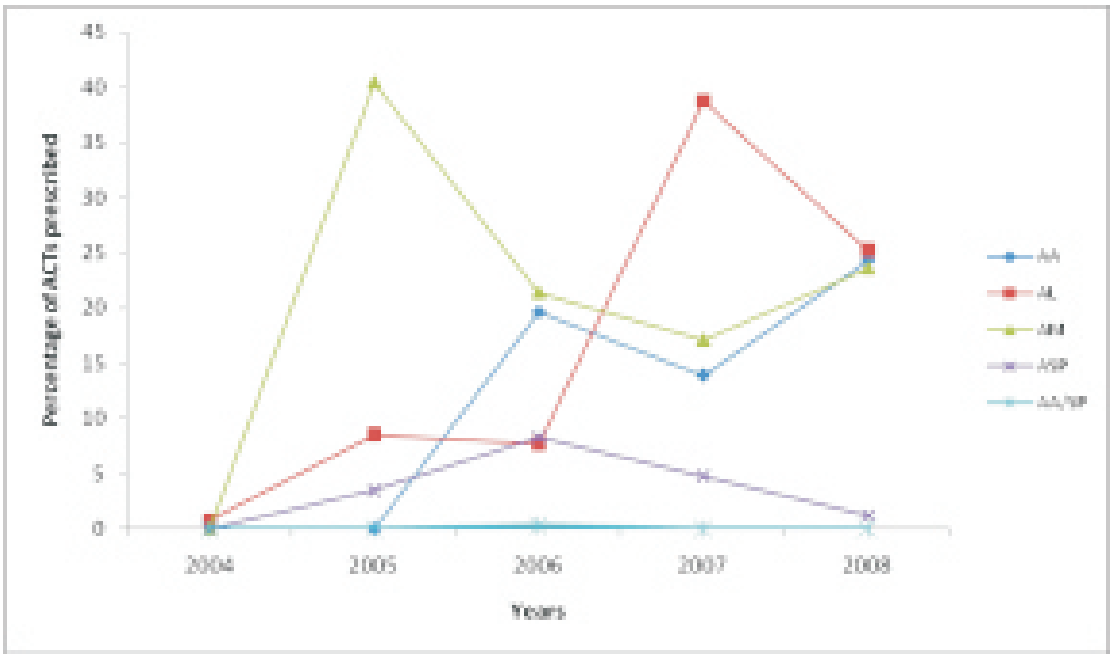

Figure 1: Trend in ACTs Prescribed from 2004 to 2008.

Discussion

This study showed a wide variation in the antimalarials prescribed which continued three years into the change of the national antimalarial policy. This may reflect the challenges posed by the wide range of antimalarials available in the open market and this may be an obstacle to the success of the antimalarial policy[9]. This is because with fewer antimalarials available in the market, prescribers gain more experience and are more likely to recognize drug interactions and any associated adverse drug reactions. This diversity in malaria treatment may also reflect prescriber's variability in their familiarity with the policy recommendations or inconsistency in the reference sources of their choice[10].

This study showed artesunate as the most prescribed antimalarial monotherapy prior to the policy change as against earlier studies which assessed the pattern of antimalarial prescriptions (Isah et al[10], Meremikwu et al[12], and Ogungbamigbe et al[13]) and showed chloroquine as the most prescribed antimalarial monotherapy, followed by sulphadoxine/ pyrimethamine. This observation may be explained by the progressive reduction in chloroquine prescriptions by prescribers, and their switch to better alternatives like artemisinins and its derivatives even before the change in the antimalarial policy. This reflects prescriber's awareness of the emergence of P.falciparum resistance which had become clinically apparent. The continued prescribing of chloroquine and sulphadoxine/pyrimethamine after the change in the National Antimalarial Policy (NAP) has also been corroborated by Oshikoya [14] and Etuk et al[15]. This practice may not be unrelated to the low prices of these medicines despite their failing therapeutic efficacy[7]. The World Health Organization (WHO) has however

discouraged the manufacturing and sales of artemisinin monotherapies,[16] thus appealing to pharmaceutical industries to halt their production in other to prevent development of resistance which has unfortunately been recently reported in the Thai-Cambodia border by Dondorp et al[17]. Although monotherapy prescriptions declined following the change in antimalarial policy there was an increase in the prescriptions of non-artemisinin-based combination therapy especially those containing sulphadoxine/ pyrimethamine (SP). This was similar to the finding of Meremikwu et al[12]. This development is not in keeping with the National Antimalarial Policy (NAP), which has relegated the use of SP to the arena of Intermittent Preventive Treatment (IPT) in pregnant women attending Antenatal Clinics. Three years into the change in NAP, prescribers in these government-owned Hospitals adhered to the First line Antimalarial Policy (Artemether-Lumenfantrine) in more than 70% of cases. ACTs has thus replaced Antimalarial Monotherapies as the most prescribed antimalarials in the Out-Patient Departments (OPD) in government hospitals. This is an encouraging finding suggesting that affordability was less of a factor in the acceptability of the ACTs contrary to initial fears[18-19]. On the contrary these medicines have been said to reduce the overall cost in managing malaria in a year[20], since they also provide prophylactic benefit. The high percentage of ACT prescriptions in this study may be different from those recorded in private-owned clinics, as highlighted by an earlier study[12]. Adherence to any policy may be influenced by a number of factors including clarity of guidelines, strong evidence, adequate funding, support by opinion leaders, clinical outcomes and feedback. The percentage of prescribers' adherence to Artemether-Lumenfantrine (AL) increased from 0.8% in 2004 to 25.2% in 2008, representing an increase of 24.4%. Although prescriptions of AL were on the upward trend, AL prescriptions were less than 30% of the antimalarials prescribed in 2008. This was similar to the finding by Mokuolu et al[21]. This study also identified a rising trend of non-ACT combinations for the treatment of uncomplicated malaria. Although these non-ACT combinations were cheaper than the ACTs, their prescriptions may worsen malaria morbidity due to the present level of P.falciparum resistance to them. Secondly, the useful therapeutic life of Mefloquine in the ACT combination will be compromised by increasing the selection pressures of the parasite to this antimalarial. The only non-ACT which was formerly recommended by the WHO as a temporal measure reserved for countries which for whatever reason were unable to move to the ACTs was Amodiaquine /Sulphadoxine-Pyrimethamine[22].

A major limitation of this study was that the records in the Out-Patient departments in both institutions prior to 2004 were discarded. This did not permit for data collection for the previous years. However this study has highlighted some flaws in the management of malaria by prescribers in government owned Hospitals. This has shown that training programmes directed at health service providers regarding the current National Antimalarial Policy is crucial at all levels of our healthcare. Also Continuous surveillance of rational prescription of the

ACTs and adherence to the National Antimalarial Policy should be undertaken by relevant authorities. Our Out-patient departments should also be equipped with modern record keeping methods to make for easier retrospective studies of antimalarial therapy.

Conclusion

This study showed good adherence to the change in antimalarial policy by prescribers working in public hospitals. Although encouraging, there is however a need for stiffer regulations and monitoring regarding artemisinin monotherapies if success in malaria control must be achieved in our environment.

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