



The Nigerian Journal Of PHARMACY

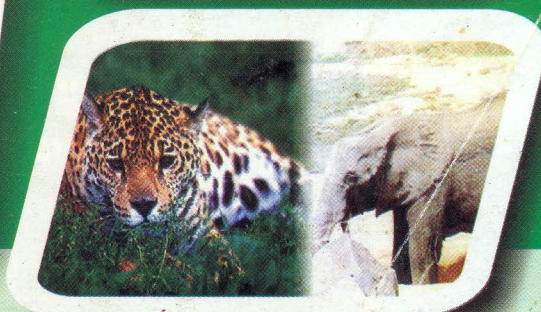
AS MEN OF HONOUR
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THE OFFICIAL ORGAN OF THE PHARMACEUTICAL SOCIETY OF NIGERIA .FOUNDED 1927

VOL. 37 January-March, 2005 ISSN 0331-670X

Cover Story

SYSTEMS BIOLOGY



Yankari 2004

- President's Welcome Speech
- Key Note Address
- Communique

HIGHLIGHTS

- The Burden of Counterfeiting of Pharmaceutical Products
 - Micro Lending and Smieis
- Effects of Microbial Contamination of Liquid Multivitamin Preparation
 - Review of Malaria in Nigeria
 - Pharm D.: To be or not to be

CONTENTS

3

EDITORIAL

5

YANKARI "2004"

6

Presidential Address at Opening of Yankari "2004"

6

The Burden of Counterfeiting of Pharmaceutical Products

9

Micro Lending and SMIES: Capacity Building for Pharmacist and Small Scale

Pharmaceutical Industries

14

Pharmacists and Public Health: The Bamako Initiative Revisited

17

Communique

21

COVER STORY

23

Systems Biology

23

PUBLIC HEALTH/NATIONAL NEWS

27

The Polio War: Finishing Strong

27

New Population Policy Launched

27

Healthy Eating: Fish

27

PSN National Treasurer Launches Health Magazine

28

ORIGINAL RESEARCH

29

Colorimetric Determination of Tetracycline Hydrochloride with 4-

Nitrobenzenediazonium hydrogen sulphate

29

Effects of Microbial contamination of Liquid Multivitamin preparations

37

Factors Affecting Practice - Area Choices by Pharmacy Students in Nigeria

41

REVIEW

45

A Review of Malaria in Nigeria

45

CONTINUING EDUCATION

53

Herb and Drug Interactions: "Natural" Products are not always safe

53

VIEW POINT

55

Pharm D: To be or not to be!

55

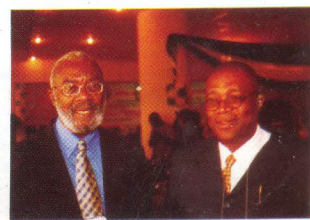
INFORMATION DESK

56

INFORMATION TO CONTRIBUTORS

58

Yankari "2004" in retrospect



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THE OFFICIAL ORGAN OF THE PHARMACEUTICAL SOCIETY OF NIGERIA .FOUNDED 1927

On Monday, the 31st of January 2005, the Minister of Health announced the removal of chloroquine as first line treatment of malaria in Nigeria and the adoption of the artemisinin-based combination therapies (ACTs) as advocated by the World Health Organization. The selected ACTs are co-formulated Arthemeter + Lumefantrine and Artesunate + Amodiaquine. While this was shocking to some people, it was good news to others.

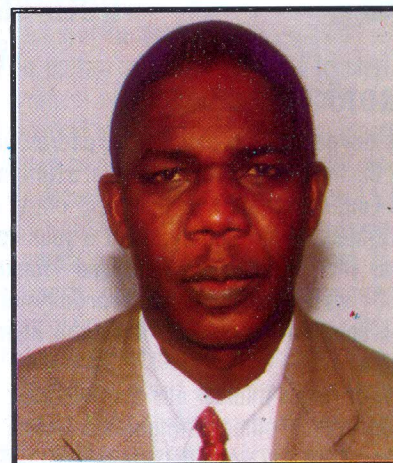
For most Pharmaceutical Companies, whose product portfolio includes chloroquine in many different formulations; tablets, syrups, capsules and caplets as well as the injectables, the news was anything but good. However, for those Companies that are into importation of artemisinin-based antimalarials, it was good news indeed.

The Minister declared that his Ministry was ready to support Pharmaceutical Companies that are ready to work towards production of ACTs locally in order to improve availability. The National Institute of Pharmaceutical Research and Development (NIPRD) also declared that the plant *Artemisia annua*, was already being grown in its facility, and it is available for those who need it.

Malaria has the following global epidemiological statistics. Nearly 500 million people suffer from acute malaria each year: the majority of victims are children, with at least 1 million deaths attributable to malaria occurring every year, mostly in under 5's and pregnant women. 40 percent of the world is at risk of malaria but 9 out of 10 cases occur in Africa south of the Sahara. The economic cost of malaria in Africa south of the Sahara is valued at \$2 billion each year. 5.3-school age years child are lost each year and a workday loss of 121 days per worker per year has been established. Considering the burden of malaria on the people and the economy on one hand, and the fact that most Nigerians are said to be living below the poverty line, the adoption of the more expensive artemisinin-based combination therapy raises some questions, which are hereby highlighted.

Currently, the availability of the ACTs leaves much to be desired. Only few Companies are currently producing or importing any of the artemisinin-based therapies. Considering the magnitude of the malaria problem, Nigerians must have a drug that they can find to purchase easily or at least with minimal stress.

Another close factor to availability is affordability. The cost price for treatment of one episode of malaria using the artemisinin-based combination therapies is an average of 1,000 naira (artemisinin mono products are between 400 -600 naira) compared to about 70 naira (maximum) for



Dr. Anthony Ogbeche
Editor-in-Chief

chloroquine treatment. Not many people can afford to spend so much money on treating malaria for one person. Thus, the item is not available for purchase in enough Pharmacies around the Country and when available, the cost of the item prevents a good percentage of the population from acquiring it. We can therefore say that ACTs are not accessible.

Closely linked to affordability and availability is the formulation factor. Initially, only injectable forms of ACTs were available. Later a few companies began the importation and local packaging of some oral formulations. Till now a lot of the ACTs available are the injectables raising other issues such as who and where it can be administered, safety and sterility, HIV infection, pain and discomfort, etc.

Another factor to consider is the dosing schedule for ACTs. Compared to chloroquine in which drugs are given for a maximum of 3 days, and usually once daily with the 2-2-1 formulations, most ACTs are taken for between 5 - 7 days as two stat, then once daily. Compliance will therefore be a very big issue and a serious point during counseling sessions with clients. With 3 days dose of chloroquine, people found it difficult to finish their drugs not to talk about 7 days dosing for ACTs. Also because ACTs act very rapidly reducing parasitaemia to low levels from the first dose, it means the patient already feels much better but he has 5 or 6 days of drugs to go. The problem of remembering to use the drugs each day becomes a serious burden for the patient.

These various issues must be articulated properly and considered by the Transition Committee to be set up by the Minister. Thus the adoption of ACT and its full integration requires a very carefully planned and executed machinery.

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A REVIEW OF MALARIA IN NIGERIA

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ABSTRACT

Malaria is an important disease in developing countries. It causes significant morbidity and mortality, especially to children and pregnant women. Currently the anti-malaria policy is being reviewed and so this article is written with the view of refreshing our knowledge about malaria and highlighting some salient issues pertaining to the effect of anti-malarials on the heart.

KEY WORDS: Malaria, Anti-Malarials, Drug effects on the heart.

INTRODUCTION

Malaria is an important disease in developing countries. In 2001, UNICEF opined that more than 700,000 lives of children below the age of five were lost to malaria in Africa meaning that a child died of malaria disease every 30 seconds¹. Disease due to malaria is on the increase in Nigeria and other Sub-Saharan areas of Africa, carrying along with it high morbidity and mortality rates. It accounts for the greatest singular cause of morbidity and mortality in Nigeria. About 30 percent of children under the age of five in Nigeria die from malaria every year. The disease is responsible for potential medical complications such as low birth weight in infants, increase in sudden abortion and stillbirths in pregnant women. Given the fact that about 46 percent of an average household income is expended on treatment of malaria, the disease is a major cause of poverty in Nigeria². 40 per cent of the world's population lives in areas with high malaria prevalence². Although malaria presents these impressive figures, there is a broad therapeutic arsenal against it and in order to use them wisely, the knowledge of their side effect, including effects on the heart, is vital. UNICEF noted that the greatest challenge to malaria control is that the cheapest, anti-malaria drug, chloroquine, was rapidly losing its effectiveness in many endemic areas of the world¹. As a matter of fact the Federal Ministry of Health in Nigeria announced the ban of chloroquine as first line therapy for malaria in a news broadcast

announcemeed on Monday, 24th January 2005 and carried by most daily newspapers³.

The malaria burden on African countries in terms of cost far exceeds 1% of the GDP per year, with the attendant appreciable physical debility and serious constraints in private investment. Malaria, though widely distributed all over the world, the order of prevalence is: Africa>India-Asia>South-America>Srilanka>Vietnam, Solomon Islands varying focally from country to country^{4,5}. A geographical area is called endemic when it shows constant incidence of malaria cases with natural transmission continuing through the year. The degree of endemicity is variable and can be expressed as the splenic index, or the number of subjects with palpable enlargement of the spleen when examined. Manifestation of the disease in different populations is very much influenced by the extent of interaction between some determining factors such as humans, parasite, vector and the environment in the different localities. In much of Africa, young children and pregnant women are the most afflicted whilst in Asia adults as well as children are equally affected⁶.

NIGERIA - EPIDEMIOLOGY OF MALARIA⁷

The vectors - *Anopheles gambiae*, *Anopheles arabiensis* and *Anopheles funestus* are thought to be the main culprits in malaria transmission in Nigeria. They survive and breed in fairly clean sunlit small water pools. They abound also in wells, water cisterns and water storage tanks, which are known common features of both urban and rural areas in the country.

Epidemiologically, malaria in Nigeria can be described as holoendemic, implying an intense all year round malaria transmission with greater intensity in the wet season than the dry season. During peak transmission, over 70% of children aged 1-10 years suffer high rates of disability with the associated high parasite density and splenomegaly, whereas the adult population enjoys high levels of immunity. About 95-99% of the adult population are known to be carriers of the

malaria parasite with less than 30% of this figure coming down with illness.

There are four species of the genus *Plasmodium* responsible for the malaria parasite infections that commonly infect man, *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*⁸. The main culprit of all four species of malaria parasite is *P. falciparum*, which is responsible for almost 90% of malaria infection. *P. malariae* occurs in about 6-8 percent of cases and *P. ovale* in 1-2 percent. About 15-20 percent are thought to be due to a mixture of *P. falciparum* and *P. malariae*. A paucity of information exists for *P. vivax* malaria in Nigeria.

THE MALARIA INFECTION^{2,9}

The extent and degree of malaria infection may be sequel upon rate of transmission, which in turn depends on the concurrent presence of three indispensable elements:

1. The parasite, plasmodium, present in various forms of development in humans with active malaria
2. The vector, anopheles mosquito, the female insect feeds on human blood, takes up and carries for life the gametocyte
3. The receptive humans; children and younger population comprise the most receptive subjects due to underdevelopment and low immunity, and are actively involved in malaria transmission. Adults in malarious regions tend to develop some measure of immunity rather readily as a result of previous repeated infections.

Other factors such as climate and environmental conditions (temperature and humidity) have an appreciable influence on the life of the vector insects and on the development of malaria parasites. *P. falciparum* and *vivax* show no sporogonic activity (that is, transformation and maturation of sporozoites in the mosquito) at temperatures below 20°C, at higher temperatures, sporogony also decrease with increase in temperature. The longevity of the anopheles is equally influenced by relative humidity: the lower the humidity, the shorter the life span of the insect and this

ultimately effects sporogony leading to marked drop in malaria transmission.

LIFE CYCLE OF THE HUMAN PLASMODIUM¹⁰

There are two phases to the life cycle of the malaria plasmodium, the anopheles mosquito (invertebrate) phase and the human (vertebrate) phase.

The Invertebrate phase is also called the sexual or sporogonic cycle. The onset of this phase is characterized by the ingestion of human blood containing male (micro) and female (macro) gametocytes after a bite of a patient with malaria by the anopheles mosquito. In the gut of the mosquito, the gametocytes emerge from the parasitized erythrocytes, the female gametocyte develops directly into a single macrogamete, the male gametocytes undergo very rapid nuclear division and emits 8 flagellate filaments each containing a nucleus, which then separate from the microgametocyte body and develop into microgametes. The microgamete, propelled by its flagellum, moves towards the macrogamete and penetrates it to form the zygote or fertilized ovum. The zygote develops into a mobile ookinete within 24 - 28 hours of fecundation and migrates towards the wall of the middle intestine where invagination of the mucosal surface commences leading to migration to the outer surface. There is further development into an immobile oocyst with accompanying synthesis of a cystic wall. A proliferation process ensues with the loss of apical apparatus, and mitotic activity of the nucleus with associated subdivision of the cytoplasm into lobes, each endowed with a portion of nuclear material and the formation of spherical buds. Sequel upon this proliferation stage is the reconstitution of the apical complex and the eventual formation of the sporozoites. These separate from the sporoblast buds, emerging free in the mosquito's colon, and concentrating in the insects' salivary glands. The sporozoites become more virulent, mature into the infectious forms and then migrate to the salivary ducts ready to be injected into man. The entire developmental processes takes between 7 and 28 days.

The Vertebrate phase, the asexual or schizogonic cycle, begins with a mosquito bite

and the associated injection of infectious sporozoites. These invade the liver via the blood stream within a few minutes. Within four hours of inoculation, the parasite begins to show changes similar to those associated with other transitional phases from invasive to proliferative forms. In the course of maturation to exo-erythrocytic schizonts, the pattern of development is akin to that of oocyst formation. The mature merozoites separate to invade the blood stream. Because of their short life span, they rapidly attack the erythrocytes within minutes of their release into circulation. By chemotaxis, the parasite readily recognizes the red blood cell (RBC), attaches itself to it and finally penetrates it. Subsequent upon the invasion of an erythrocyte, the parasite undergoes repetitive cycles. Within the erythrocyte the parasite loses the apical apparatus and acquires a ring-like globular shape. The parasite draws mainly on hemoglobin as nutrient by endocytosis while digestive and metabolic residues give rise to haemozoin, the characteristic pigment of malaria parasites. The mature schizont structurally occupies most of the erythrocyte leading to rupture of the erythrocyte membrane and release of merozoites into the blood stream, which then attack new red blood cells. The liberation of merozoites from ruptured RBCs coincides with the clinical manifestation of the malarial attack or rigor.

LABORATORY DIAGNOSIS OF MALARIA⁸

The diagnosis of malaria is confirmed by blood tests and can be divided into microscopic and non-microscopic tests.

Microscopic Tests: These involve staining and direct visualization of the parasite under the microscope and include the Peripheral Smear Test and the Quantitative Buffy Coat Test (QBC).

The Peripheral Smear Test: This is usually used and routinely performed in hospitals and laboratories around the country. Both the thick and thin films are used though the thick films yield higher results. Sometimes, no parasites can be found in peripheral blood smears from patients with malaria, even in severe infections. This may be explained by partial anti-malaria treatment or by sequestration of parasitized cells in deep vascular beds. In these

cases, parasites or malarial pigment may be found in the bone marrow aspirates. Presence of malaria pigment in circulating neutrophils and monocytes may also suggest the possibility of malaria.

The Quantitative Buffy Coat Test: The QBC involves collection of 20ul of blood in a capillary tube, which is pre-coated with acridine orange, and its centrifugation. The infected RBCs are pressed to the wall of the tube by a small float. The DNA of the parasite takes up the acridine orange stain and when viewed under an ultraviolet light source, it fluoresces. The stained parasites appear as 'stars in a sky'.

Non-Microscopic Tests: These tests involve identification of the parasitic antigen or the anti-plasmodia antibodies or the parasitic metabolic products. They include Para Sight F test (which involves a dipstick antigen capture assay, using a monoclonal antibody against *P. falciparum* histidine rich protein-2 [pfHRO-2]¹¹). It is rapid, sensitive and specific for *P. falciparum* and The Immuno Chromatographic Test (which is an in-vitro immuno diagnostic test for the detection of circulating antigen of *P. falciparum* or *P. vivax* in whole blood. It is rapid and does not require specialized equipment.

Other tests include:

- * Optimal Assay
- * Polymerase Chain Reaction
- * Detection of antibodies by Radio immuno-assay, immuno-fluorescence or enzyme immuno-assay.

The simplest and surest test is, however, the time honored peripheral smear study for malaria parasite. However, it is necessary as Pharmacists to know of useful additional tests that are available.

A positive diagnosis is made from laboratory investigations. However, when laboratory facilities are not available a diagnosis must be made on the clinical manifestations and history. In endemic areas, the onset of intermittent fever accompanied by splenomegaly and other characteristic symptoms should suggest diagnosis of malaria.

ROLL BACK MALARIA INITIATIVE

The Roll Back Malaria (RBM) initiative is a creation of the World Health Organization (WHO). Dr. G. Harlem Brundtland, the Director-General of WHO, announced it at the World Health Assembly in May 1998. RBM aims to coordinate global action in the fight against malaria and help governments reach their own individual targets to combat the disease in their country¹². The RBM partnership includes governments, development agencies, commercial organizations, professional associations, civil society, research groups and the media. RBM will provide overarching coordination of all efforts at malaria control; it will promote the development and better utilization of all tools for malaria control as and where appropriate, and it will help strengthen the health sector. But it will be driven by the countries¹³. Tools for malaria control that will be implemented through networking include insecticide-treated bed-nets, rectal suppositories, the package of essential interventions for care of the sick child, simple packaging of anti-malarials to help ensure people take the proper course of treatment, improved referral for severe malaria by mothers and traditional healers and training of drug suppliers in provision and counseling for safe use of anti-malarials. In 2000 April, the African Summit on Roll Back Malaria was held in Abuja. Thus, for the first time, many nations gathered to discuss, plan, review and look for the way forward about the scourge of malaria.

OBJECTIVES OF RBM

The goal of RBM is graded or progressive. It does not assume that malaria could be eradicated at a go. Global strategies on malaria include:

- * Disease management (early diagnosis and immediate treatment to prevent complications; patient education and health education of the populace; rational use of anti-malarial drugs, and immediate referral as and when necessary)

- * Disease prevention (prophylactic use of drugs; use of insecticide-treated nets (ITNs); environmental management; hygiene; etc)

- * Operational Research

There are six elements of RBM and include:

- ❖ Rapid diagnosis and treatment
- ❖ Better multi-pronged protection using ITNs, environmental management to control mosquitoes and making pregnancy safer
- ❖ Focused research to develop new medicines, vaccines and insecticides and to help epidemiological and operational activities
- ❖ Coordinated actions for strengthening existing health services, policies and providing technical support
- ❖ Evidence based decisions using surveillance, appropriate responses and building community awareness
- ❖ Harmonized actions to build a dynamic global movement.

Multiple Prevention Element of RBM¹⁴

This element contains measures for mosquito control in the right mix for the local situation as well as safer pregnancy in which women are able to take anti-malaria drugs. However, the use of insecticide treated nets (ITNs) is novel and is being pushed vigorously as a method for significantly breaking the transmission of malaria. Studies so far have shown that malaria incidence can be significantly reduced in the community when ITNs are used. Cost has, however, remained a problem and its use can only be enhanced when it is affordable. The net is treated with lambda-ghalotrin (25g/liter), which comes in a 1-litre pack costing approximately N10,000. This can be used to treat 140-200 bed nets. A net pack for a single bed will cost approximately N145 while the cost for one for a double bed is N700-800. Net re-treatment is 6-monthly to maintain effectiveness. However, the Society for Family Health is marketing a brand of ITN, which can last for up to 4 years before re-treatment is necessary.

THE ROLE OF PHARMACISTS IN RBM¹⁵

The Pharmacist has an important role to play in RBM since drug use is one of the main thrusts of malaria control. The Pharmacist should be actively involved in the following activities:

1. Developing (with other health professionals) an anti-malaria first aid kit fitted with equipment for simple diagnostic tests and affordable drugs for early treatment for every household especially for

the "at risk" group.

2. Improving anti-malarial drug use all over the country and assessing the benefits of such improvements.

3. Making visible efforts in public understanding of the value of ingesting the full regimen of anti-malarials in order to achieve complete cure. Simple technologies e.g blister packaging should be developed to achieve maximal compliance.

4. Exerting more efforts to reduce the presence of fake or substandard drugs in the market.

5. Improving drug use through packaging, public information and assessment of quality of drugs.

6. Counseling mothers on home treatment of malaria which is one of the strategic activities of RBM in the communities.

7. Developing repositories which contain well-characterized parasites from treatment failures and successes, taking into account the recognition of drug distribution and use to monitor resistance (inter-sectoral collaboration essential for this).

8. Ensuring sustainable quality assurance system. The overall goal is to guarantee a zero-defect product to the consumer and the communities.

9. Strengthening the consortium of pharmacology, pharmacy and Pharmacognosy, traditional and herbal medicine centers doing clinical studies for the discovery, design and development of new anti-malarial drugs.

10. Agreeing on what the pharmacists want for waiver of tax in order to bring down the cost of drugs.

MANAGEMENT OF MALARIA²

Anti-malaria drugs currently in use for the successful management of malaria in humans display quite extensive and varying activities against various species of plasmodia and various stages of parasite development. From the chemotherapeutic standpoint, anti-malarial drugs are classified into four main groups.

1. Tissue Schizonticides

These are drugs capable of acting on tissue schizonts, especially liver schizonts. These may be further subdivided into:

- ❖ Primary or pre-erythrocytic

schizonticides which are active on the parasitic forms prior to the invasion of the RBCs;

❖ Secondary or exo-erythrocytic schizonticides which act on the exo-erythrocytic forms and thereby prevent recurrences typical of infections with *P. vivax* and *P. ovale* e.g. proguanil

2. Blood Schizonticides

These drugs act upon the asexual forms of the parasite in the blood, which are responsible for initiating malarial attacks and therefore produce a cure that may be radical (*P. falciparum*, *P. malariae*) or only clinical unless anti-recurrency drugs are administered concomitantly (*P. Vivax*, *P. Ovale*). Chloroquine is a good example though resistance to it by the protozoa is affecting its usefulness.

3. Gametocides

These act on the sexual forms of the parasite in the blood and so prevent the diffusion and migration of these forms in the blood. Different gametocides are known to demonstrate different and varying effects on the different species of plasmodium; only Primaquine is known to be active on all species.

4. Sporontocides

These act by inhibiting the sporogonic cycle in the mosquito that has sucked blood from a gametocyte carrier treated with such drugs. These drugs render gametocytes infertile rather than act gemetocidally.

ANTIMALARIALS

Classification of anti-malarials:

- * Cinchona alkaloid e.g. Quinine, Quinidine
- * 4-aminoquinolones e.g. Chloroquine, Amodiaquine
- * 8-aminoquinolone e.g. Primaquine
- * Quinoline-methanol e.g. Mefloquine
- * Acridine-based e.g. Mepacrine (Quinacrine, Atabrine)
- * Biguanides e.g. Chloroguanide (Proguanil)
- * Diaminopyrimidines e.g. Pyrimethamine, trimethoprim
- * Sulfonamides and Sulfones e.g. Sulfadoxine, Sulphamethopyrazine, Dapsone

* Phenantrene-methanols e.g. Halofantrine

* Sesquiterpine lactone e.g. Artemisinin, Artemeter, O; hydroartemisinin.

CHLOROQUINE

Chloroquine was first synthesized in 1934 as a 4-aminoquinolone. It has been broadly used in the clinical setting of malaria disease due to its pharmacokinetic features which give a more useful posology (half life of about three to five days), low toxicity (can be used in pregnancy) and therapeutic effectiveness in various tropical areas, even with reports of increasing resistance in many cases of severe malaria^{16,17}.

As stated in the introduction, chloroquine is being withdrawn as first line treatment for malaria in Nigeria because of reported widespread resistance and a new anti-malarial policy is being formulated. The World Health Organization (WHO) guidelines on malaria control stipulates that adequate clinical and parasitological response levels less than 75% should be addressed by a drug policy review. The results of a drug efficacy testing done across the six geopolitical zones in the country gave a national average of 39.2%³, therefore making a review of the anti-malarial treatment policy necessary. It was stated that similar reviews have been conducted in several other African countries in East, Central and West Africa. These countries similarly adopted the Artemisinin-based combination therapy as new first line therapy³.

Acting as an erythrocyte schizonticide, chloroquine is effective against the four known strains of plasmodium species and as a gametocide; it is effective against *P. vivax*, *P. ovale* and *P. malariae* except in areas where resistance is now a major problem.

Chloroquine is one of the drugs most widely used in the world, representing approximately 80% of the global consumption of antimalarials¹⁸. Its adverse effects are infrequently observed when using therapeutic doses, being of little clinical significance. The most frequent of these are dyspepsia, pruritus (frequently related to dark skin), psoriasis exacerbation and neuropsychiatric disturbances (vertigo, insomnia), photosensitivity, myopia, agranulocytosis and aplastic anemia. The main side effects described are related to the

use of high doses and for long periods of time, for example, administration of chloroquine for more than five years in a dose greater than 100 grams in adults. An example of which is in the treatment of rheumatoid arthritis, where it can frequently cause irreversible retinopathy, even after discontinuation of the drug. Myopathy, even cardiac myopathy can occur in patients using high doses¹⁶. The use of this drug is not prohibited in pregnancy, as there are no reports of teratogenicity with its use. Considering that during the second trimester of pregnancy, the primigravida, even if semi-immune, can develop severe forms of malaria, the use of chloroquine in these cases remains effective if resistant strains are not encountered¹⁷. The prophylactic use of chloroquine does not inhibit the humoral response to the yellow fever vaccine. Chloroquine taken orally is usually well tolerated by patients. Nausea, vomiting and fatigue are relatively common symptoms that do not limit its usefulness.

Parenteral chloroquine is a potent vasodilator so hypotension that follows its parenteral administration is an expected consequence with use of high concentrations of the drug.

In a study¹⁹, three healthy individuals were submitted to chloroquine prophylaxis and it was shown that they had transient abnormalities in their electrocardiogram (T wave with diminished amplitude and Qtc interval prolongation) without clinical manifestations. There are also some reports of sudden deaths after the use of intramuscular chloroquine in children with severe malaria, probably because of cardio toxicity. Reports about the acute complications of the use of chloroquine were not found.

QUININE & QUINIDINE²¹

Quinine is one of the oldest anti-malarials, its medical use being reported about 350 years ago. It is the main cinchona alkaloid, though quinidine also has anti-malarial activity. The re-emergence of quinine in malaria chemotherapy is as a result of recent developments of *P. falciparum* resistance to mainly chloroquine and sulphadoxine/pyrimethamine, and also to the fact that quinine is very effective in cerebral malaria. Quinine is an active blood

schizonticide in all forms of human malaria. It is thought to share the same mechanism as chloroquine. Commonly administered form is oral; and after dosing with 600mg peak plasma concentration of 2mcg/ml is reached in 2 to 3 hours. Subsequent 600mg given 8 hourly affords maximum blood concentration of 16-21 mcg/ml.

It rarely causes untoward cardiac effects (except when therapeutic levels are exceeded). Cardiac arrhythmias and severe hypotension were reported whenever the drug (endovenous presentation) was administered quickly. The most frequent cardiac arrhythmias are sinoatrial block, junctional rhythms, atrioventricular block, ventricular tachycardia and ventricular fibrillation. During quinine administration, the Qtc interval should be monitored likewise when administering its isomer, quinidine. In cases of an increase in the Qtc interval above 25%, the administration rate should be lowered²⁰.

Quinidine is an optic isomer of quinine and has its greatest importance in the treatment of arrhythmias (Quinidine is a 1A class anti-arrhythmic agent). Quinidine is even more effective than quinine in the treatment of resistant forms of malaria, however, it is obviously more cardio toxic. Due to its widespread use as an antiarrhythmic, quinidine is usually more available than quinine especially in developed countries where malaria is more infrequently diagnosed. This feature of quinidine was responsible for its substitution in the parenteral treatment of malaria in America. It characteristically produces lengthening of the Qtc interval of the electrocardiogram in 1-3% of patients and it can even cause ventricular arrhythmias and syncope (the right treatment being administration of magnesium sulphate intravenously). Quinidine can also slow cardiac conduction to a point where it will cause cardiac blocks.

HALOFANTRINE

Halofantrine is an anti-malarial drug initially identified by the chemotherapy programme of the Second World War. It however, did not see the light of day because of the effectiveness of chloroquine in management of malaria. The post-war declining fortunes of chloroquine²² led to the

marketing of Halfan(R) by SmithKline and French Laboratories in 1984. Halofantrine is a blood schizonticide and quite effective against multi drug resistant *P. falciparum*. It acts on both the trophozoites and schizonts in the blood cell. It however, shows erratic and unpredictable absorption profile and since no parenteral formulation is available, critically ill patients who cannot take oral medication may not benefit from it. It is administered in 3 doses of 500mg each (or 8mg/kg body weight in children) at 6-hourly intervals.

Since the beginning of its clinical use, evidence of its effects in cardiac conduction has accumulated, it prolongs the QTc interval even in therapeutic doses, in a dose dependent manner. Because of these features, it is contraindicated in patients with a history of prolongation of QTc interval, with clinical conditions that increase the QTc interval duration (myocardial disease, electrolyte disturbances, thiamine deficiency and concomitant use of other drugs that also affect the QTc interval), and in patients with cardiac abnormalities. Previous evaluation with an electrocardiogram is needed in order to screen for people with congenital long Qtc interval syndrome (also known as Romano-Ward syndrome). In spite of its rarity, severe rhythm disturbances were reported in people with this syndrome using halofantrine. The cardiovascular effects of this drug are quinidine-like as quinidine and halofantrine have similar chemical structures.

In high doses, ventricular arrhythmias can be seen^{23,24,25,26}.

ARTEMISININ^{2,27}

Also known as Quinghaosu, artemisinin is an active principal of a Chinese medicinal herb called *Artemisia annua*-Compositae, which has been used in the treatment of fever in China for more than 1000 years.

Artemisinin, a sesquiterpene lactone, with an internal peroxide linkage was isolated as the main component of *Artemisia annua* by Chinese scientists about the year 1972. It demonstrated potent and impressive anti-malarial activity; however, formulation problems led to the development of arthemeter and artheeter and dihydroartemisin, a lactone reduced analogue of artemisinin. The peroxide linkage of artemisinin and analogues have been shown to be very essential for anti-

malarial chemotherapeutic activity as the deoxy derivatives devoid of the Endoperoxide Bridge lack any activity.

The anti-malarial action of artemisinin-based compounds depends on two steps: the first step is activation, comprising the iron-mediated cleavage of Endoperoxide Bridge to generate an unstable organic free radical and/or other nucleophilic species. The second step is an alkylation step, which involves the formation of covalent adducts between the drug and malarial parasite proteins. After the drug has been converted to reaction radical, it can then form covalent bonds with protein.

Arthemeter is safe at low doses, showing relatively low clinical toxicity²⁸. In high doses, its toxicity is mainly on the neurological system and not the cardiovascular system. An animal study has demonstrated neurological toxicity associated with the prolongation of the QTc interval in laboratory rats treated with an artemisinin by-product²⁹.

PRIMAQUINE

Primaquine is the only drug effective against exo-erythrocytic forms of *P. vivax* and *P. ovale*. The mechanism of action is thought to resemble that of quinolone derivatives, i.e formation of DNA-complex in the plasmodium protozoa; and like quinine it causes partial clumping of haemzoin pigment. It also interferes with redox systems in mitochondria³⁰.

Its overdose can cause hypotension and cardiac arrhythmias, which are rare. Gastrointestinal disturbances and blood disorders are more common³¹.

MEFLOQUINE

Mefloquine is a highly active blood schizonticide and is thought to act, in part, by impairing oxidation of parasite membrane NADH. It may also share with the 4 quinolones, an ability to interfere with parasite digestion of hemoglobin by binding ferriprotoporphyrin.³² It is highly lipophilic, hence the extensive tissue distribution which is responsible for the relatively long elimination half-life of about 20 days.

Mefloquine is a synthetic anti-malarial drug that is effective as single dose against multi drug resistant malaria in man.

Mefloquine can produce sinus

bradycardia and sinus arrhythmia and should not be used in patients on beta-blockers. Its combination with other anti-malarials increase cardiac toxicity and seizures³³.

OTHER ANTIMALARIALS³⁴

These agents do not have significant cardiac effects.

QUINACRINE

Quinacrine is a blood schizonticide which is no longer used as an anti-malarial. It is an acridine derivative which is administered orally as a yellow powder. Common adverse effects include nausea, diarrhea, headache and insomnia, with larger doses producing dermatitis and toxic psychosis. It produces a marked additive action with 8-aminoquinolones, thus generally increasing the risk of toxicity.

PROGUANIL

Proguanil (chloroguanide) is an effective prophylactic agent against falciparum malaria but it is not fully effective against vivax malaria. It acts against the exo-erythrocytic stages preventing the development of the merozoites. Proguanil is not used in acute malarial attacks because of its slow onset of action, even though it is active against the asexual stages of all species. Proguanil hydrochloride is administered to non-immune individuals in prophylactic dose of 100 mg per day orally. Adequate protection is given to semi-immune individuals by a weekly dose of 330mg. When used to treat acute attacks of vivax malaria, it is administered in an initial dose of 300 to 600 mg followed by 300mg daily for five weeks. With long term prophylaxis, a common side effect is anorexia, possibly due to the inhibition of gastric secretion. Other adverse effects include headache in large doses, vomiting, abdominal pain and diarrhea.

SULFADOXINE

A combination of 25 mg pyrimethamine and 500 mg sulfadoxine (fansidar) is used to effect a radical cure, as well as in suppressive therapy, especially in chloroquine resistant P.

falciparum. Adult dose is 3 tablets at once given by the oral route. It can also be given by the intramuscular route. Treatment is once.

DAPSONE

Dapsone belongs to the Diaphenylsulfone group of drugs. It is mainly used as an anti-leprosy agent. It is however, effective in some cases of P. falciparum and in chloroquine resistant areas.

DISCUSSION

In order to save a large percent of the nation from the problems of malaria, various approaches have been tried. The recent RBM initiative is a most laudable project if effectively managed. If the problem of malaria is comprehensively taken care of, more healthy people will be available to work at their jobs, more children will be in school and more money will be available for other needs in households as well as for public and private life. To be able to curtail the morbidity and mortality due to malaria, all health care personnel must be on the front line of the fight. Knowledge of the life cycle of the mosquito, the vectors and hosts for the malaria parasite is useful in control. This review has helped to update the knowledge of the Pharmacist and other associated health care workers in order to enable a more informed strategy against the scourge of malaria.

The review also includes the effect of anti-malarial agents on the heart. Heart complications are on the increase in Nigeria according to reports³⁵. Once cardiac arrhythmia is exacerbated or cardiac rhythm is in any way adversely affected, the aim of treatment would be to improve cardiovascular function either by restoring sinus rhythm or by controlling ventricular rate, or by conversion to a more desirable pattern of electrical and mechanical activity. Pharmacists need to be up-to-date on the effects of these anti-malarials on the heart in order to help clients that visit the pharmacy and not further compromise their cardiac function, as the pharmacy is the first port of

call for many persons seeking health care³⁶. The Pharmacist should ask the patient about other diseases or infections he is being treated for and drugs that he is currently using for those diseases or infections. A patient that already has a cardiac disease such as hypertension, arrhythmias, etc must have judiciously selected anti-malarial drugs dispensed to him in order not to worsen his condition.

CONCLUSION AND RECOMMENDATION

In conclusion, malaria is indeed a major problem in developing countries like Nigeria and an effective, integrated approach is the only way to ensure that control is achieved. Pharmacists must ensure that they help their clients by not offering them anti-malarial drugs that would further worsen an existing cardiac complaint nor initiate a cardiac problem in clients without a pre-existing cardiac disorder.

Recommendations include:

- ❖ Environmental control should be enforced to reduce growth and maturation of the mosquito.
- ❖ The new anti-malarial policy should be produced speedily and disseminated to every health care worker especially those involved in primary health care.
- ❖ Pharmacists should be actively involved in the Roll Back Malaria Initiative.
- ❖ Local sources of the proposed artemisinin-based combination products should be made available to consumers.
- ❖ Economic incentives should be given to pharmaceutical companies for importation of artemisinin products that have the capacity to produce ACTs locally.
- ❖ Update lectures should be conducted to ensure that all health care providers are exposed to the most current information about transmission, resistance to drugs and treatment available per time as well as adverse and side effect profiles of the anti-malarial drugs.

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