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HEAVY UNCONTROLLED USE OF CHLOROQUINE MAY HAVE CONTRIBUTED TO THE DEVELOPMENT OF RESISTANCE BY *PLASMODIUM FALCIPARUM*: A WARNING TO THE OBSERVED USE OF THE NEW ARTEMESIN GROUP OF DRUGS.

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ABSTRACT
Severe malaria is a medical emergency requiring the urgent administration of an effective antimalarial drug. Chloroquine was such a drug, being very effective in the clearing of the causative agent of malaria known as *Plasmodium falciparum*. The operational use of anti-malarial drugs has unfortunately been hampered by the development of drug resistant plasmodium malaria. Resistance to chloroquine is the most important unwholesome incidence of impediment as this has been documented in many countries. Resistance to other alternate antimalarial drugs has followed in many countries of the world. There is subsequently a concern about the artemesinin group of drugs which are the first-line antimalarial drug at the moment. This study calls attention to the protection of this group of drugs from mis-use and hence, from development of plasmodium resistant malaria.

KEYWORDS: Malaria, resistance, chloroquine, artemesin.

INTRODUCTION

Severe malaria is a medical emergency requiring immediate administration of a rapidly effective antimalarial drug. For many years, chloroquine was essentially the main stay of malaria treatment, being effective in eliminating *Plasmoduim falciparum* – the commonest malaria parasite in our environment. Chloroquine is less toxic than the other anti-malarial drugs such as quinine and is possibly more rapidly effective if the infective strain of *Plasmodium falciparum* is sensitive. However, chloroquine resistance is now so prevalent that most physicians would prefer to use other anti-malarial agents (Olatunde, 1977; Eke, 1979; Ezedinachi, *et al.*, 1991; Hagos, *et al*., 1993).

There has also been demonstrated resistance to other drugs such as mefloquine (Salako and Fadeke-Aderoummu, 1987), sulphadoxine/ pyrimethamine and quinine (Adegu, *et al*., 1995).

Self medication and treatment before presentation to hospital is extremely common and drugs such as chloroquine are bought across the counter without prescription for the treatment of fevers and suspected malaria. Malaria fever, which relapses after a recent course of medication, is probably caused by a parasite resistant to that drug. Since chloroquine was then the most commonly and widely used first-line treatment for malaria, it follows therefore that those patients would have probably taken chloroquine at home.

In a study conducted at the Baptist Medical Centre, Eku, Nigeria, on under-five aged group, who were exclusively diagnosed and treated for malaria, it was found that chloroquine was the most frequently bought and used agent by patients and their attendants from across the counter (Table 1).

About 55.4% of the patients had bought and taken chloroquine at home before arrival to the hospital. This agrees with the findings of Warrell (1983), who noted that most patients, who needed quinine therapy, would already have failed to chloroquine therapy.

This action of buying chloroquine from across the counter may have contributed to the spreading of resistant strain of *falciparum* malaria. Resistant parasites are selected when parasites are exposed to sub-therapeutic drug concentrations. This occurs if there is a widespread use of drug, and if doses are

Table I: Frequency of the type of drug taken before presentation to the hospital.

DRUG	FREQUENCY	PERCENT
Quinine	12	6.2
Chloroquine	108	55.4
Analgesics	44	22.6
Local herbs	5	2.6
Unknown	26	13.3
Total	195	100

Table 1 shows high rate at which chloroquine is bought across the counter by the citizens.

inadequate or if there is poor compliance. It is also inevitable if the drug is eliminated slowly from the body.

Slowly eliminated drugs such as mefloquine, with a half-life of three weeks or chloroquine, with a half life of two months, persist in the blood and act as a selective pressure for months after drug administration.

In Africa, approximately 250,000 kg of chloroquine was consumed annually (White, 1996). Thus, in many parts of the continent, the majority of the citizens had chloroquine in their blood at any one time (White, 1996). Chloroquine also causes pruritus in dark-skinned patients and may be dose-limiting leading to incomplete dosing of the drug (White, 1996).

Added to these was the problem of adulterated anti-malarial agents in the society exposing patients to sub-therapeutic drug concentration.

The first-line regimen for malaria now is the Artemesin Combined Therapy (ACT). Presently, there are several brands of this drug and many more may be manufactured, all properly regulated by NAFDAC. This group of drug is available over the counter and sales are often made neither without prescription nor with proper diagnosis made to rule out other causes of a fever. This is the same problem that chloroquine had.

Koram, e*t al*., (2005), recently showed that ACTs are very effective agents for the curing of patients with malaria, and that making them the first-line drugs for the treatment of uncomplicated malaria as a step in the right direction. However, they noted that the problem of not having a fixed-dose regime of the combination poses a major challenge in terms of treatment adherence (compliance) thereby influencing the progression of drug resistance.

The World Health Organization (WHO), has since 2001 recommended that countries where malaria is resistant to conventional treatment such as chloroquine should switch to ACTs. Forty countries, with twenty of them being in African, have adopted their recommendation (WHO, 2004).

Subsequent to this advise, the WHO has also called on the manufacturing companies to produce artemesin with combined formulation and not as the monotherapy package, because of the risk of developing drug resistance (Jackson, *et al*., 2006).

It is reported that many African countries such as Sudan, have therefore banned the importation of artemesin monotherapies, but many have not (Passi, 2006). The recommendation of marketing only the combined formulation is to prevent the development of drug resistance. But currently, there are both the monotherapy and the combination therapy available in our environment.

We also call on the appropriate authority to look into the packaged artemisin monotherapy as Jackson et al., (2006) reported some treatment failures because they found that a large number of artemesin – based drugs on sale in Africa do not obey the WHO recommendation in terms of treatment duration, and even a few packages contained fewer pills than indicated in the manufacturers leaflet.

Drugs that are sold already packaged with insufficient tablet to make up a therapeutic course carry a risk of treatment failures. The WHO recommends seven days duration of treatment with the artemisin monotheraphies because shorter courses result in unacceptably high rates of relapses. The artemisin – based combination treatment is to be used for three days (Jackson et al., 2006).

Oduola, *et al*. (1992) demonstrated a disturbing but though a transient resistance to artemesin. They suggested that the dispensing of new anti-malarial drugs should be closely monitored in order to protect their clinical usefulness. This short letter is a clarion call to the urgent need for all regulatory agencies to enforce the use of artemesin group of drug so as to protect against the development of resistance known to contribute to the failure of chloroquine chemotherapy.

The Roll Back Malaria (RBM) is the current WHO initiative that is mobilizing support targeted to meeting local malaria control need. This initiative emphasizes the use of insecticide – treated nets (ITN) as one of the key strategies for malaria prevention and control in Sub-Saharan Africa (Jones, 2000). Their use is to be encouraged in our region with its high intense all year round malaria transmission, since they will help reduce the burden of malaria and thereby reduce the need for a continual usage of the ACTs.

We cannot let artemesin fail. The next good drug for malaria may be many “light” years away. We must therefore protect ARTEMESIN.

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