International Scholars Journals

African Journal of Malaria and Tropical Diseases ISSN 2736-173X Vol. 13 (3), pp. 001-004, March, 2025. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Efficacy of Chloroquine in Treating Uncomplicated *Plasmodium falciparum* Malaria in Northwestern Nigeria

Bello SO[1,2] *, Muhammad BY[1], Bello AY[3], Ukatu AI[4], Ahmad BM[5], Adeneye AA[1,6], Cherima JY[7]

[1]Department of Pharmacology, Usmanu Danfodiyo University Sokoto, Nigeria.
[2]Karaye Hospital, P.O.Box 1522, Sokoto, Nigeria.
[3]Sokoto Specialist hospital, Sokoto, Nigeria.
[4]Mayo Clinic and Maternity, Birnin Kebbi, Nigeria.
[5]Women and Child Welfare Clinic, Sokoto, Nigeria.
[6]General Hospital, Tanghaza, Nigeria.
[7]General Hospital Wurno, Sokoto, Nigeria.

Accepted 19 January, 2025

The pattern of infection and *in vivo* response of uncomplicated *Plasmodium falciparum* malaria to Chloroquine as first line drug and Quinine, Halofantrine or Sulfadoxine-Pyrimethamine as second line medications was evaluated at nested sentinel points, including Government and Private Practices, for three consecutive months. 559 cases were evaluated of which 22.5% failed on Chloroquine therapy. The age range of *P. falciparum* malaria cases was 4 months to 48 years, with a mean and median age of 9.2 and 3 years, respectively. There were significantly more female patients than male. Also, ages 5 years and below accounted for 63.2% of cases and as a group had an increased risk of treatment failure with Chloroquine compared to older patients. In general, male patients also had a higher relative risk of treatment failure on Chloroquine. Patients treated in Government practices were more likely to fail than those treated in Private practices. All cases of failure to Chloroquine treatment responded to Quinine, Halofantrine or Sulfadoxine-Pyrimethamine.

Key words: *Plasmodium falciparum* malaria, Chloroquine, resistance.

INTRODUCTION

Chloroquine, a 4-aminoquinoline, remains the most prescribed antimalarial medication in Sub-Saharan Africa in spite of reports of increasing resistance to it by *Plasmodium falciparum (Pf)* (WHO, 2003) . This may not be unrelated to its cheapness, low side effect profile, availability and the longer experience with its use. It has recently been argued that the use of CQ as first line medication may be associated with increased risk of mortality from *Pf* malaria at all age, but especially in children less than 5 years of age (Zucker et al., 2003). Intuitively, it may be expected that such risk may be related to the prevalence of CQ resistance in the practice zone. Furthermore, the WHO recommends that an antimalarial agent may not be used as first line medication when the level of resistance is above 25% in an area (WHO, 2001). Another attraction to complying with this recommendation is the recent suggestion that such discontinuation of use may result in recovery of CQ sensitivity and reduced prevalence of CQ resistance transporter gene mutation in *Pf* (Toshihiro et al., 2003).

*Corresponding author. Tel: +23460230450 (Office), +2348035073372 (Mobile). E-mail: bellooricha@yahoo.com, bello@rclmail.com.

Abbreviations: CQ, Chloroquine; *Pf*, *Plasmodium falciparum*.

To the best of our knowledge, the level of *in vivo* resistance of *Pf* to CQ has not been defined in northwestern Nigeria. It may be important to estimate the prevalence of CQ resistance in this region as a guide to defining clinical treatment algorithm, government policies and managing drug resistance. However, the interactions that lead to clinical efficacy are tripartite and include drug, host and parasite factors (Pratt, 1990). It may be important to co-evaluate some of these factors in an efficacy study. Such efficacy evaluation is probably best conducted to reflect real time clinical setting. 'Real time' may be defined as study designs that contain not too restrictive inclusion criteria and include data from Government and non Government health facilities. This study was therefore carried out to establish the efficacy of CQ in northwestern Nigeria in 'real time' clinical situations.

MATERIALS AND METHODS

Setting

Two types of clinical practices were used; Private (PP) and Government (GP). For this study, we defined PP as health facilities that are owned by individuals, or sponsored by a non Government organization (NGO) alone or in conjunction with a Government agency and with at least a fully qualified and duly registered consulting physician and at least a community health assistant or pharmacy technician dispensing drugs. We defined GP as any practice completely owned by any level of Government or its agency and fulfilling other criteria as defined for PP. Two neighboring northwestern Nigerian states (Sokoto and Kebbi States) were selected by convenient sampling. Practices were identified from the Hospital registers of the respective state ministry of health and appropriately assorted as private or Government then listed and coded. The codes were then randomly selected (using random number tables), up to a pre-specified number of 2 PPs and 4 GHs (for logistic reason and because on the registers, there were roughly twice as much GPs that fit our inclusion criteria as PPs). The Medical directors of selected practices were then approached for consent to participate in the study. If not given, another practice of similar classification was again randomly selected. The study was thus carried out at the following sites concurrently; Mayo Clinic and Maternity Home, Birnin Kebbi (PP), Sokoto Specialist Hospital, Sokoto (GP),

Women and Child Welfare Clinic, Sokoto (GP), General Hospital Tanghaza (GP**)**, Karaye Hospital, Sokoto (PP), General Hospital, Wurno (GP). At each study point, Ethical approval was obtained from the local standing committee. For the whole study, ethical consultation (Reither-Theil, 2001) was used.

Study Protocol

This study was carried out using the standard WHO Guidelines for Good Clinical Practice (WHO,1995) and the WHO protocol for assessment of the therapeutic efficacy of antimalarial drugs (WHO, 1996) . In this protocol, while age less than 5 years is the preferred focus because higher mortality is recorded below that age, a provision is made that alternatively all age groups may be included. The research team including the clinicians from the PP was trained on the WHO protocol to the satisfaction of the principal investigators. Consecutive patients of all ages presenting from 1st September 2003 to 31st November 2003 at the participating clinics with axillary temperature above 37.5^{o}C and peripheral smear positive on Leishman Stain for *Pf* were enrolled into the study after written informed consent if adult or from parents of minors. Patient who requested specific antimalarials that was not CQ, who had taken another antimalarial or herbal medication claimed to be efficacious for malaria, who self reported pruritis or non specific adverse event with previous experience on CQ, who had been on long term CQ for non malarial illnesses or who had to be placed on multiple drug regimen for confirmed or suspected concurrent infection, pregnant women, lactating women and patients evaluated as having severe or complicated malaria as defined by the updated WHO criteria (WHO, 2000) were all excluded from the study. Microscopy and classification of resistance was done according standard WHO recommendation (WHO, 2001). CQ was given as 25 mg/kg in divided doses over 36 h orally or parenterally (intramuscularly/ subcutaneously at age below 1 year) according to clinical status at first contact or patient's preference. In cases of CQ resistant malaria, or where CQ could not be continued because of adverse drug reaction, any of Quinine, Halofantrine or Sulfadoxine-pyrimethamine was given as second line medication at standard doses. Halofantrine was an option only for patients above 15 years of age.

Outcome measures

Primary outcome measures were allocated a binomial grouping of either clinical sensitivity to CQ or resistance (pooled RI, RII, and RIII). Secondary outcome measure was response to second line medication. Host factors considered were age and sex.

Statistics

Both *MINITAB* and *Analyze-it for Microsoft Excel* Statistical software were used for the data analysis. The relationship between response to CQ and age was evaluated by binary logistic regression and that between sex, age group and response to CQ resistance was evaluated by Fisher's exact test and again by binary logistic regression after ranking CQ sensitivity and resistance (Resistance=1 and Sensitivity = 2). Subset analysis was done for age equal to or less than 5 years and age equal to or more than 40 years. These ages were decided by epidemiological dictum and quartile analysis respectively. Within variable comparison of proportion was done by the 1 binomial proportion tests or Chi-Square. Alpha was set at < 0.05.

RESULTS

A total of 560 patients participated in the study. One had some missing data and 559 qualified for analysis. Of these, 302 (54.0%; 95% CI 50.0 to 58.2) were female and 257(46.0% 95% CI 51.8 to 50.2) were male and this difference was significant (P=0.007). The age range was 4 months to 48 years, mean: 9.2 years, standard deviation =11.8 years and median: 3 years. 353 (63.2%; 95% CI 59.0 to 67.2) were age 5 years or below; of these174 (49.3%; 95% CI 43.6 to 54.6) were female and 179 (45.3 %; 95% CI 45.3 to 56.0) were male. The difference was not significant (p= 0.57). 20 (3.6%; 95% CI 2.2 to 5.5) were age 40 years and above. The age distribution is positively skewed (Skewness=1.504 at p< 0.0001 and Kurtosis=1.418 at p=0.02) and with multiple

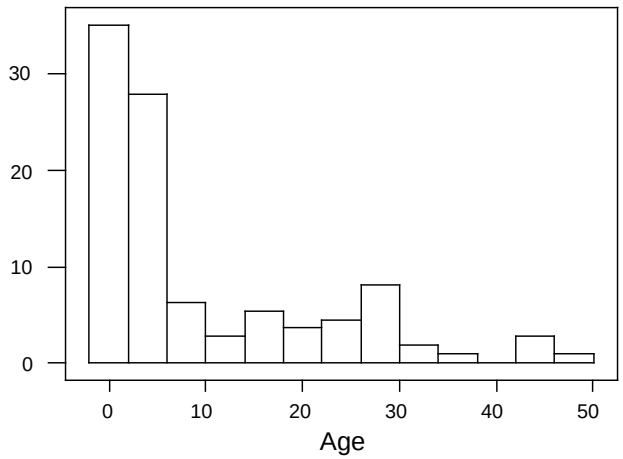

Figure 1. Incidence of *P. falciparum* malaria by age in the study sample.

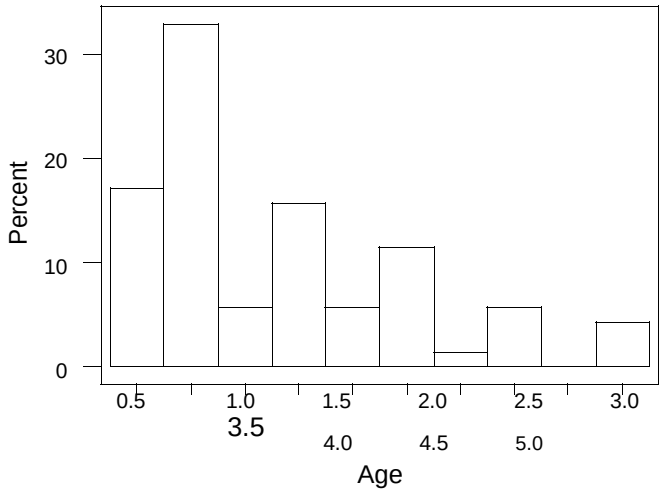

Figure 2. Incidence of *P. falciparum* malaria by age in the age range 5 years and below.

peaks; one major peak incidence in the age range 0-5 years and another at 25-30 years (Figure 1). This skewness and multiple peaks were maintained in subset analysis of sites, sex, and age but was most striking in the under 5 years subset (Figure 2) . In the latter case, the major peaks are 0.5 to 1 year and 2 to 3 years. The age range of uncomplicated *Pf* malaria that presented in GH in the period of study was 4 months to 15 years, while the age range in PP was 4 months to 48 years.

Of the 559 patients, 126 (22.5%, 95% CI= 19.1 to 26.2) had *in vivo Pf* resistance (RI, RII or RIII) to CQ (subsequently labeled CQR). 57 (18.9%; 95% CI 14.6 to 23.6) of the females and 69 (26.9%; 95% CI 21.5 to 32.7) of the male had CQR. The sex difference in CQR was significant (p=0.025). Males appear to carry an increased risk of CQR; Relative risk 1.42 (95% CI 1.10 to + ; p=0.02) while the females have a reduced risk; Relative risk 0.70 (95% CI 0.00 to 0.91; p=0.02). Independently, age apparently does not influence response to CQ; Odds ratio 0.98 (95% CI, 1.02, 1.07) but on subset analysis, in the age group 5 and below, 94 (26.6%; 95% CI 22.1 to 31.6,) had CQR compared to 32 (15.5% 95% CI 10.9 to 26.2) of the ages above 5 year. The relative risk of CQR at age 5 years or below over older age group was 1.71(95% CI 1.27 to + ; p=0.002). However, in the 5 year or below age group, the risk of CQR in male compared to female was not significant; relative risk 1.11(95% CI 0.83to + , p=0.33) . Power and sample size analysis revealed that this study is sufficiently powered (above 0.60 at the alpha of 0.05) only to detect sex differences in resistance to CQ in the age 5 years and below at and above 25%. Also, 26.5% (95% CI 18.0, 37.0) resistance was recorded at the GP but 20% (95% CI 12.0, 29.1) at the PP. The relative risk of CQR in the GP over the PP was 1.30 (95% CI 0.65 to 2.6). All the CQ failures responded to the second line medications.

DISCUSSION

Pf malaria apparently affects the lower age groups in all age ranges tested and in either sex. Although this may represent background skewness in age distribution at the community level, the consistency of this observation in all subset analysis make this an unlikely explanation. It probably represents an increasing level of acquired immunity with advancing age possibly due to repeat infections. In this regards, the peaks in the age distribution might suggest that immunity to *Pf* waxes and wanes at the early ages, becoming more established at later age (above 30 years). The absence of cases in the age range below 4 months and above 48 years in the 3 months of study may represent the low incidence in this age group due to immunity acquired *in utero* at the lower age and cohort effect plus herd immunity at the higher age. Alternatively, or additionally, it may reflect more severe infections and mortality at these age ranges. On the basis of relative incidence alone, it appears that the ages 5 years and below should be the focus in malaria intervention in the study area. This may be important considering that until few years ago, vaccines and new therapies are traditionally not evaluated in this age group for ethical concern (NIH, 2001). It appears that older patients with uncomplicated *Pf* malaria cases prefer PP while pediatric age group present at both PP and GP. This may be because in the study zone, GPs have dedicated pediatric units while PPs do not. Alternatively, it may suggest that at the current level of health awareness, PP may be a preferred treatment point if facilities are considered equal by the public. This has important implication for control programs and suggests that NGOs should be involved. That there appear to be a higher risk of uncomplicated *Pf* malaria in male but that

this risk is not different in the 5 years or below may be due to socio-cultural factors where non pediatric age females are more likely to be treated at home than in hospitals.

The high rate of CQ resistant *Pf* malaria in the study area is disturbing. At 22.5% average resistance and a 95% CI that includes and exceeds the WHO recommended 25% limit for change in therapeutic algorithm, it might be important to consider changing CQ as the first line drug in the study area. However, it may be argued that the consequence of resistance to CQ may be a better guide in considering such a change in policy. It is reassuring that all cases of resistance to CQ responded to Sulfadoxine-Pyrimthamine, Halofantrine or Quinine. In this regard, it may be important to note that CQ has a long half life (10 to 24 days), and may synergize with the second line medication. This study suggest that by itself age might not be an important host factor in the outcome to CQ therapy but that ages below 5 years as a group has a higher relative risk of resistance . This suggests that another factor(s) common to this age group might be responsible. Pharmacokinetic or maternal acquired factors may be important. The male sex and treatment in a GP appear to be independent risk factors for resistance to CQ. In the former, the 'male physiology' may be the important difference. Male hormone may either suppress important immunological co-factors to drug response or the female hormones may be protective to infections by resistant strains of *Pf*. The observation that this risk is not maintained at age 5 years and below when sex specific hormones are at lower levels further support this suggestion. Alternatively or in addition, male related surface antigen expressed on red cells or immunocytes may be the important interaction. In this case, maternal factors acquired *in utero* might explain the absence of this risk in the lower age group. The influence of site on CQR may be confounded by the demographic difference in patients or related to socio-economic parameters and patient-physician rapport, all known to influence treatment outcome but not evaluated in this study. However, these are intuitively expected to favor PPs.

This study suggest high level of *in vivo* resistance to CQ by *Pf* in the study area and proposes that male sex and age below 5 years are important factors dictating treatment outcome in uncomplicated *Pf* malaria infection. The draw back is the use of sentinel points, which may have some selection bias a priore'. For example, most CQ treatment of malaria may be outside the clinic setting and are never recorded because outcome was successful. Thus CQR may actually be lower in the study population. Furthermore, the brand of CQ used in this study was not standardized which could be important since studies have shown that over 48% of the drugs in Nigeria are of low quality or outright fake (Taylor et al., 2001; Shakoor, 1997). This may also artificially elevate CQR. However, non–standardization of CQ best reflects real clinical practices in the study area. Moreover, in the study by Taylor et al. (2001), CQ samples average above the pharmacopoeial limits and no sample assayed less than 95%. This reassures that treatment failure due to pharmacopoieal issues probably contributed little in this study. Within these limits, this study presents a de facto evidence of high level of CQR while acknowledging that the pathway to observed response may be multifactorial. It remains important to carry out further studies to clearly define such factors.

REFERENCES

National Institute of Health (2001). Policy and Guidelines on the inclusion of Children as participants in Research Involving Human Subjects. http://grants1.nih.gov/grants/guide/notice-files/NOT98-024.html.

Pratt BW (1990). Origin of Acquired Drug Resistance. In : Pratt BW , Taylor P (eds) Principles of drug Action-the basis of pharmacology. 3rd edn. Churchill Livingstone Inc, New York, pp 565-567.

Reither-Theil S (2001). The Freiburg approach to ethics consultation: process, outcome and competencies. J. Med. Ethics 27:i21-i23.

Shakoor O, Taylor RB, Behrens RH (1997) Assessment of the incidence of substandard drugs in developing countries. Trop. Med. Int. Health 2:839-845.

Taylor RB, Shakoor O, Behrens RH, Everard M, Low AS, Wangboonskul J et al (2001), Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. Lancet 357:1933.

Toshihiro M, Akira K, Lum KJ, Bwijo B, Takechi M, Zungu I I et al (2003). Recovery of Chloroquine Sensitivity and low prevalence of the *Plasmodium falciparum* Chloroquine resistance transporter gene mutation K76T following the discontinuance of Chloroquine use in Malawi. Am. J. Trop. Med. Hyg. 68(4): 413-415.

World Health Organization (2003). Africa Malaria Report 2003. http://www.rbm.who.int/amd2003/amr2003/ch3.htm.

World Health Organization (2001). Monitoring Antimalarial Drug Resistance. http://www.who.int/emc.

World Health Organization (2000). Severe falciparum malaria. Trans. Roy. Soc. Trop. Med. Hyg. 94 (Suppl): S1/1-S1/90.

World Health Organization (1996). Management of uncomplicated malaria and the use of antimalarial drugs for the protection of travelers. WHO/MAL/96.1075.

World Health Organization (1995). Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical report Series, Number 850, WHO, Geneva.

Zucker JR, Ruebush II TK, Obonyo C, Otieno J, Campbell CC (2003). The mortality consequences of the continued use of Chloroquine in Africa; experience in Siaya, Western Kenya. Am. J. Trop. Med. Hyg. 68(4): 386-390.