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RESISTANCE PATTERNS OF *PLASMODIUM FALCIPARUM* MALARIA TO CHLOROQUINE IN KAMPALA, UGANDA
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RESISTANCE PATTERNS OF *PLASMODIUM FALCIPARUM* MALARIA TO CHLOROQUINE IN KAMPALA, UGANDA

H. G. MULINDWA, H. MAYANJA-KIZZA and J. FREERS

ABSTRACT

Background: **Chloroquine is a first line drug for the treatment of uncomplicated *Plasmodium falciparum* malaria in Uganda. Recently, there have been increasing reports of resistance of *Plasmodium falciparum* malaria to chloroquine, as well as an increase in malaria morbidity and mortality among adults and children.**

Objectives: **To assess the current effectiveness (clinical and parasitological response) of chloroquine in the treatment of uncomplicated *Plasmodium falciparum* malaria, and to define the magnitude of chloroquine resistant *Plasmodium falciparum* malaria in Kampala.**

Design: **A descriptive cross-sectional study among adults and children.**

Setting: **Mulago hospital complex (the national referral and teaching hospital in Kampala, Uganda) between September 1998 and March 1999.**

Results: **Ninety six patients with *Plasmodium falciparum* parasitaemia of 1000 to 100,000/µl of blood were treated with oral chloroquine phosphate, and followed up for 14 days. Sixty three (65.6%) patients showed clinical improvement, 29 (30.2%) deteriorated and four (4.2%) had no change. Adequate parasitogical response was seen in 71 (74 %), moderate in four (4.2%) and poor in 21 (21.8%) patients. Treatment failures were highest among children below five years, with eleven (57.9%) children not responding to chloroquine.**

Conclusion: **Although chloroquine was found to be effective in two thirds of all patients, the high treatment failure, especially seen in children below five years is of concern. This necessitates further countrywide studies, and possibly a need to review the use of chloroquine as single first line drug for the treatment of uncomplicated malaria in Uganda, especially in children below five years of age.**

INTRODUCTION

Recently, an increase in cases of clinical malaria admitted to Mulago hospital in Kampala has been observed. Many of these patients probably have chloroquine resistant malaria. According to the Ugandan Ministry of Health, chloroquine is still the first line drug for the treatment of uncomplicated *Plasmodium falciparum* malaria(1). However, many clinicians have expressed concern as to whether chloroquine should still be used as the first line treatment. This has resulted in the increased use of alternative treatment protocols for malaria, and use of newer drugs for fear of possible resistance to chloroquine(2). In addition there is a lot of self-medication by rural and urban dwellers, who use anti-malarials indiscriminately, often with sub-optimal doses(1). The observed apparent increase in the incidence of malaria may be due to: (i) a reflection of a real increase in malaria incidence and severity in the country, (ii) use of incomplete treatment regimens in the community; (iii) poor response of malaria to chloroquine and; (iv) use of poor quality antimalarial drugs. Up to 30% chloroquine tablets and 33% injectable chloroquine used in Uganda contain less than the expected amount of the active ingredient(2).

In this study, we evaluated the responsiveness of uncomplicated *Plasmodium falciparum* malaria to oral chloroquine among adults and children in Kampala, Uganda.

MATERIALS AND METHODS

In this study, the protocol designed by the malaria control unit in Uganda, in collaboration with the World Health Organisation (WHO), which set terms of reference for researchers assessing the therapeutic efficacy of anti-malarial drugs was used. The protocol has been designed for use in anti-malarial responsiveness studies in Uganda(3). The assessment is based on the oral administration of a standard dose, of 4-aminoquinolines, administered according to body weight, and follow up for 14 days. It may not be necessary to determine serum drug levels and urinary metabolites of chloroquine in this assessment, and a history of prior administration of 4-aminoquinolones is not an exclusion criteria.

Examination of blood slides: Blood films for malaria parasites were prepared directly from capillary blood (finger prick) or from sequestrene anti-coagulated venous blood, where

films were made within one hour of collecting the blood. Two thin films (to determine the species of plasmodium) and two thick films (for parasite counts) were prepared and fixed with absolute methanol (methyl alcohol). Malaria parasites were stained with Fields' stains A and B. The number of asexual parasites in the fields having 100 white blood cells (WBC) was counted. The total white blood cell count (WBCC) was also determined. The parasite count was estimated using the formula:

$$\frac{\text{WBCC/µl x Parasites counted against 100 WBC}}{100}$$

Study population. Most of the study subjects were recruited from Kampala's population of about one million inhabitants. Every second patient presenting with suspected malaria with a positive screening thick blood film was selected for further evaluation. Those who subsequently showed *Plasmodium falciparum* malaria in the thin blood films, and counts of 1,000 to 100,000 asexual parasites/µl of blood on thick blood film(4) were eligible for enrolment into the study. (Many patients with film confirmed malaria in Mulago hospital had less than 1,000 malaria parasites/µl of blood).

Exclusion criteria: Patients with severe complicated malaria were excluded from the study. These included patients with: (i) more than 100,000 asexual parasites/µl of blood; (ii) inability to drink or breast feed; (iii) persistent vomiting; (iv) recent history of convulsions; (v) lethargy or the unconscious state; (vi) inability to sit or stand up and; (vii) an axillary temperature above 40°C. Also excluded were patients who had other definite causes of fever. Finally, the study was restricted to those, who were able to come back for follow up visits and had easy assess to the study site.

Intervention and outcome: Eligible consenting patients were given the standard treatment of oral chloroquine base 150 mg (Avoloclor®, Imperial Chemical Industries, England). The dose was 10 mg/kg on day 1 and 2, and 5mg/kg on day 3 as recommended by the WHO guidelines (WHO/MAL/1996.1077 protocol). Children had the tablets cut up, and administered with a little water through a syringe. On day 4, 7 and 14, the patients clinical and parasitological assessment was repeated, and chloroquine responsiveness and resistance were determined.

Alternative treatment was given on day 4, 7 or 14 in cases of treatment failure. Sulfadoxine/pyrimethamine (Fansidar) tablets or syrup was given in patients with uncomplicated malaria who did not respond to chloroquine, while quinine injection, tablets or syrup was given to patients who developed severe or complicated malaria, as recommended by the Uganda Malaria Control Unit, Ministry of Health(1). Side effects of chloroquine such as vomiting, abdominal pain, itching, photophobia, hypersensitivity skin reactions, hypotension and dizziness were looked for and managed accordingly, or the medication was stopped.

Clinical response: Three categories of clinical response were used, namely: (a) a decrease of clinical score; (which refers to improvement of clinical condition); (b) no change of clinical score, (which is equivalent to no change in clinical condition); (c) an increase of clinical score, is an arbitrary approximation of severity of clinical signs based on general state of the patient, ability to feed, presence of anorexia and vomiting and axillary body temperature. In the context of overall therapeutic response, only two clinical responses were considered: namely, improvement of clinical condition (a decrease in clinical score) and no change or deterioration of clinical condition (no change or increase in clinical score).

Parasitological response: There were three categories of parasitological response. In type A, parasite count on day 4 of treatment was less than 25% of the count on day 1, and no parasites on day 7. In type B, parasite count on day 4 was less than 25% of the count on day 1, and parasites were present on day 7. Type C, was when parasite count on day 4 was more than 25% of the count on day 1(3).

Overall therapeutic response: There were three categories of therapeutic response: adequate clinical response (ACR), where parasitaemia on day 4 was less than the counts on day 1, and no parasitaemia on days 7 and 14, or parasitaemia on day 14, but clinical score less than the score on day 1. Early treatment failure (ETF) where parasite count on day 4, was greater than 25% of the count on day 1, or development of criteria of severe or complicated malaria on day 4 or before, with parasitaemia. Late treatment failure (LTF) where parasite count on day 4 was less than 25% of the count on day 1 and parasites were present on day 7, with the clinical score on day 7 greater than the score on day 1; or parasites present on days 7 and 14 with clinical score on day 14 greater than score on day 1; or development of danger signs or other signs of severe or complicated malaria after day 4 in the presence of parasitaemia.

This classification leaves out an unclassifiable category of patients who on day 4 have a parasite count of less than 25% of that on day 1, no parasites on day 7 and parasitaemia on day 14. These are expected to have re-infection(3).

Data management and analyses: Data were analysed using the computer EPI-INFO 6 program. Chi-square testing was used to test associations between different variables, with p value of less than 0.05 considered statistically significant.

Ethical issues: The study was approved by the Mulago hospital and Makerere University ethical review committees, as well as the Uganda National Council of Science and Technology. Confidentiality was maintained, and all interviews were conducted in private.

Limitations of the study. Patients did not have tests for urinary metabolites of antimalarials to determine whether the subject, had not taken any anti-malarial in the past seven days. No active measures were taken to prevent re-infection other than the usual public health measures.

RESULTS

Patients presenting at Mulago hospital with parasitaemia of between 1000 to 100,000 asexual parasites/µl of blood, and without severe or complicated malaria were studied. A total of 126 patients were enrolled, of whom 30 were excluded for failure to complete the study. Ninety six patients (76.2%) were followed up to completion of the study and were entered in the analysis. The patients ages ranged from 0.5 to 65 years, mean (± standard deviation, SD 19.9±14.5) years. Sixty four (66.7%) patients were females. Most of the patients, 55 (57%) were above 14 years of age, 22 (30%) were above five and up to 14 years and 19 (23%) were 0.5 to five years, a ratio of about 3:1:1. The majority of the patients, 89, (92.7%) were from Kampala district, where the study hospital is located.

Clinical presentation. Axillary temperature above 37.2°C was present in 90% of children up to five years, and in 71% of patients above 14 years. The mean (± SD) temperature was 38.1 ± 0.4°C, with a range of 36 - 39.5 °C. The difference between the mean temperatures on day one

among the three different age groups was not significant. Headache was present in 27% patients over14 years, but no children up to five years complained of headache.

Parasite counts on day one. The mean parasite count at enrolment was 38,600 (range 1000 - 76,200 parasites per µl of blood. There was no significant difference in the parasite counts between the different age groups or sexes at presentation.

Response to chloroquine treatment: The symptomatic response to chloroquine is shown in Table 1. By the end of chloroquine treatment, most patients did not complain of fever anymore. Itching was noted in four patients, and all responded well to chlorpheniramine.

Clinical response: Seventy eight per cent of patients above 14 years improved on chloroquine, whereas over 50% patients below five years of age deteriorated, and required alternative treatment (Table 2). Children of five years and below had a significantly higher proportion of clinical treatment failure (57.9%) compared to those above five and up to 14 years (45.4%) and adults (21.8%). Among patients who improved, the temperature decreased from an average of 38.3°C at enrolment to 36.7°C on day 4 (data not shown). However, patients who did not improve had a slight mean increase in temperature on day 4 up to 38.6°C, which later responded to alternative treatment.

Table 1

Frequency of symptoms during follow up of treatment with oral chloroquine

Symptom	Day 1	Day 4	Day 7	Day 14
Fever	74 (77%)	20 (20.8%)	10 (10.4%)	7 (7.3%)
Headache	17 (17.7%)	13 (13.5%)	2 (2.1%)	3 (3.12%)
Weakness	18 (18.8%)	10 (10.4%)	1 (1.04%)	1 (1.04%)
Anorexia	4 (4.2%)	3 (3.12%)	0	0
Vomiting	1 (1.04%)	3 (3.12%)	1 (1.04%)	0
Dizziness	3 (3.12%)	3 (3.12%)	3 (3.12%)	1 (1.04 %)
Body pains	8 (8.3%)	2 (2.1%)	0	0
Itching	0	4 (4.2%)	0	0
Insomnia	0	1 (1.04%)	0	0
Cough	1 (1.04%)	1 (1.04%)	1 (1.04%)	1 (1.04%)

Table 2

Clinical response to chloroquine. Approximation of severity of clinical signs was based on general state of the patient, ability to feed, presence of anorexia and vomiting and axillary temperature

Age (years)	All patients n=96	Up to 5 years n=19	>5 to 14 years n=22	> 14 years n=55	P value
Improved (n) %	63 (65.6)	8 (42.1)	12 (54.6)	43 (78.2)	0.008
Deteriorated (n) %	29 (30.2)	10 (52.6)	7 (31.8)	12 (21.8)	0.041
No change (n) %	4 (4.2)	1 (5.3)	3 (13.6)	0	NS

Parasitological response: The parasite response to chloroquine was significantly better among patients above 14 years compared to the other age groups (Table 3). By day 4, 55 (57.3%) patients had no detectable parasites in blood. Of these, 39 (70.9%) were above 14 years, 9 (40.9%) were 5 to 14 years, and seven (36.8%) were up to five years (data not shown). Using the WHO/MAL/96.1077 protocols classification, 49 (83%) patients above 14 years had type A response, while 11 (52.4%) patients below five years had type C response (Table 4).

Table 3

Mean parasite count. Thick blood film was examined, and parasiteamia was calculated as total white blood cell count multiplied by parasites in the field with 100 white blood cells, divided by 100

Age (years)	All patients	Up to 5 years	>5 to 14 years	> 14 years	P-value
Day 1	39,720	45,551	31,207	41,111	NS
Day 4	8,599	10,921	15,966	4,850	0.005
Day 7	1,558	2,641	3,189	530	NS
Day 14	789	1,144	41	966	0.007

Table 4

Parasitological response. Type A response is parasite count on day 4 less than 25% of the count on day 1, and no parasites on day 7, type B response is parasites on day 4 less than 25% of the count on day 1, and parasites present on day 7, type C response is parasite count on day 4 more than 25% of the count on day 1

Age (years)	All patients n=96	Up to 5 years n= 19	>5 to 14 years n=22	> 14 years n=55	P-value
Type A (n) %	71 (74)	9 (42.8)	13 (81.2)	49 (83)	0.009
Type B (n) %	4 (4.2)	1 (4.8)	2 (12.5)	1 (1.7)	0.001
Type C (n) %	21 (21.8)	11 (52.4)	1 (6.3)	9 (15.3)	0.024

Table 5

Overall therapeutic response. ACR = adequate clinical response, ETF = early treatment failure, LTF = late treatment failure. ACR = parasitaemia on day 4 less than the count of day 1 and no parasitaemia on days 7 and 14, or parasitaemia on day 14, but clinical score less than the score on day 1. ETF = parasite count on day 4 greater than 25% of the count on day 1 or development of criteria of severe or complicated malaria on day 4 or before, with parasitaemia, LTF = parasite count on day 4 less than 25% of the count on day 1 and parasites present on day 7 with the clinical score on day 7 greater than the score on day 1, or parasites present on days 7 and 14 with clinical score on day 14 greater than score on day 1, or development of signs of severe or complicated malaria after day 4, in the presence of parasitaemia

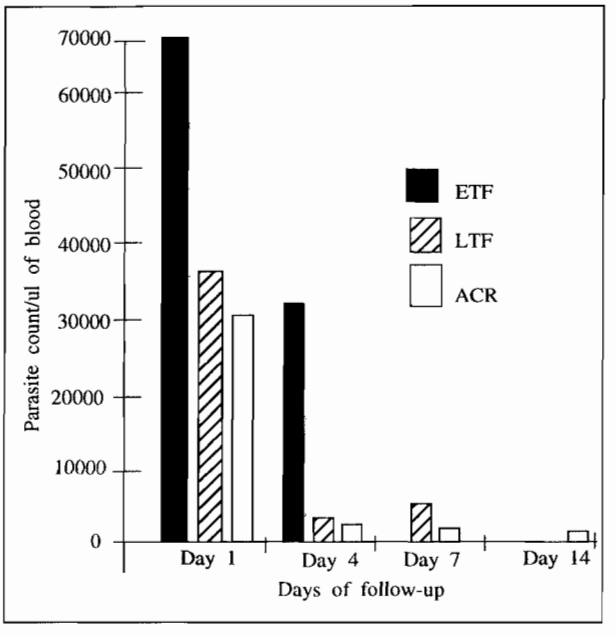
Age (years)	All patients n=96	Up to 5 years n=19	>5 to 14 years n=22	> 14years n=55	P-value
ACR (n)%	63 (65.6)	7 (36.9)	12 (54.5)	44 (80.0)	0.003
ETF (n)%	26 (27.1)	10 (52.6)	8 (36.4)	8 (14.5)	0.003
LTF (n) %	7 (7.30)	2 (10.5)	2 (9.10)	3 (5.50)	NS

Overall therapeutic response: This was determined by assessment of both clinical and parasitological response. Adequate clinical response (ACR) was highest among

patients above 14 years. Twenty six patients overall had early treatment failure (ETF) on day 4. Fifty three percent children up to 5 years had ETF, compared to 14.5% among those over 14 years of age (Table 5). Late treatment failure (LTF) was seen in only 7 (7.3%) patients overall. Patients who went on to develop ETF had significantly higher parasite counts at baseline, although this had decreased by about a half on day 4 (Figure 1). Of these 26 patients with ETF, 22 (84.6%) had type C parasitological response, one (3.9%) had type B and three (11.5%) had type A response.

Figure 1

Relationship between overall therapeutic response and parasite count. Patients with ETF on days 7 and 14, and LTF on day 14 received alternative treatment and are not included



Of the seven patients with LTF, three had type C, two type B and two type A parasitological response (data not shown). Using an arbitrary measure of dose of chloroquine per parasite, children actually seem to get less chloroquine compared to the parasite load they have, compared to adults (Table 6).

Table 6

Chloroquine was given on day 1 at a dose of 10 mg/kg body weight. An arbitrary value of chloroquine dose mg/parasite is calculated as chloroquine mg/kg body weight divided by parasites/kg body weight. Children achieve less chloroquine per parasite than adults. SD=standard deviation, kg=kilogram).

Age (years)	0.5 to 5 n=19	>5 to 14 n=22	>14 n=55
Weight (kg) mean ± SD	11.1 ± 2.7	29 ± 10.3	57 ± 8.1
Mean parasites/µl blood on day 1	45,551	31,207	41,111
Mean parasites/kg body weight	4141	1076	721
Mean chloroquine dose on day 1	110 mg	290 mg	570 mg
Chloroquine dose mg/parasite	0.026	0.27	0.79

Alternative drug use: By day 14, 33 (34.4%) patients had their anti-malarial drug changed. Almost all of the 26 patients with ETF(24) were changed on day 4 to quinine and the remaining two to sulphadoxine/pyrimethamine (Fansidar). On day 7, five patients with LTF were changed to quinine, and 2 to sulphadoxine/pyrimethamine. Finally, two patients were re-changed to quinine on day 14, after failing to respond adequately to sulphadoxine/pyrimethamine. (These two patients were siblings. Their mother (not enrolled in this study) had earlier presented in coma with cerebral malaria).

DISCUSSION

This study has evaluated the problem of response of *Plasmodium falciparum* malaria to chloroquine among patients in Kampala, Uganda. There was significant clinical resistance of *Plasmodium falciparum* malaria to chloroquine among the children aged below five years. Although fever was the main clinical feature observed, some patients presented only with non-specific complaints. These patients could have taken anti-pyretic analgesics, a common over the counter self-medication. Other symptoms such as weakness, headache, anorexia and vomiting were not as frequent as expected, and they reduced as the patients continued to improve. The exclusion of patients with severe malaria, may have been the reason for the milder symptomatology. Children had higher parasitaemia compared to older patients, but the difference between the age groups was not significant. This was also observed by Campbell and Hoffman and may explain why severe disease occurs mainly in young children(5,6). The symptomatic response to treatment showed that most of the patients had improved by the seventh day, and only 10 patients, who were apparently infected with chloroquine resistant parasites, were still febrile at that time. Symptoms of vomiting, insomnia and itching appeared on the third day of follow up, probably as side effects to chloroquine. The frequency of itching was lower than expected according to reports from general clinics, where itching is stated to be one of the commonest reasons for patient's refusal to take oral chloroquine. It is possible that those patients with prior itching after chloroquine exposure did not consent to enrolment into the study. No patients developed any serious side effects, and no deaths occurred among the study patients.

The clinical assessment of response to treatment revealed that 63 (65.6%) patients had improved by the third day of follow up and 29 (30.2%) had deteriorated (clinical resistance) on chloroquine with only four (4.2%) still having the same clinical state as on day 1. This probably implies that chloroquine is still clinically effective in two thirds of all cases, but there is resistance in about a third of the patients. Older patients had a better clinical response than the younger ones. Children aged five years and below had the highest clinical failure, followed by those above five to 14 years, and lowest among adults. This may be explained by a better immunity against

malaria in older patients, despite partial *Plasmodium falciparum* resistance to chloroquine. The overall parasitological clearance by day 4 was highest among patients above 14 years, followed by children above five up to 14 years, and lowest in those aged five years and below. It is possible that in children, an adequate MIC_{50} may not have been achieved with oral administration of chloroquine due to various reasons, such as refusal to swallow bitter crushed tablets, and later spitting out the drug. This, together with the underdeveloped immunity to *Plasmodium falciparum,* and possible partial resistance of *Plasmodium falciparum* to chloroquine may account for the poorer response in children. ACR was highest among adults and lowest in children of five years or less. Conversely, ETF was highest among the children of five years or less. Earlier studies reported higher adequate clinical response to chloroquine among children up to 12 years (81.7%), compared to results of this study (46.3%) among patients up to 14 years(7). This may suggest that in Kampala, *Plasmodium falciparum* parasites may have developed further resistance to chloroquine since 1994. There is thus need to develop alternate protocols for the treatment of malaria, especially among the younger children who have lower immunity to *Plasmodium falciparum.* This increasing resistance of *Plasmodium falciparum* malaria to chloroquine has also been seen in other countries(8-10).

Alternative treatment (quinine or sulphadoxine/ pyrimethamine) was necessary in 26 (27.4%) patients with ETF and seven (7.2%) with LTF. Although the patients put on sulphadoxine/pyrimethamine did not deteriorate to severe malaria, two were changed to quinine on day 14 due to poor response. All subjects tolerated quinine and sulphadoxine/pyrimethamine well. Patients with ETF had a significantly higher temperatures by day 4 compared to day 1. Also, the majority of subjects with ETF and LTF were still febrile by day 7 and 14 of follow up despite alternative treatment. This study was done in an urban setting and the results may not reflect the situation in the rural areas. Sezi and Ndyomugenyo found higher resistance of *Plasmodium falciparum* in urban compared to rural school children(11,12). Although there are some reports of drug resistant malaria in this country, the exact extent of this problem nationwide is uncertain. Also, studies to determine serum levels of chloroquine would be important in determining the relationship between clinical and parasitological response and chloroquine bioavailability.

CONCLUSION

Overall, chloroquine was found to be effective in two thirds of the subjects. However, the high treatment failure seen in children below five years is of concern. Since most of the patients came from Kampala district, the conclusions from this study may not be applicable to the rest of the country. A nationwide survey of the magnitude of chloroquine resistant malaria throughout Uganda is needed. The role of alternative drugs effective in treating resistant malaria also needs further evaluation. Results of this study necessitate the need to review the guidelines for the treatment of *Plasmodium falciparum* malaria for adults in Kampala. In children below five years of age, chloroquine seems to be a dangerous treatment option.

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