Effectiveness of the Use of Chloroquine plus Chlorpheniramine in the Management of Acute Uncomplicated Malaria

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SUMMARY

Objective: To evaluate the effectiveness of chloroquine (CQ) plus chlorpheniramine (CP) combination in the treatment of uncomplicated malaria in the community outside the strict follow up and compliance of hospital-based studies.

Methods: In an open randomized study, patients with symptomatic acute uncomplicated malaria in a rural community in Southwestern Nigeria were allocated to receive supervised (Group1) or unsupervised (Group2) chloroquine plus chlorpheniramine (CQ-CP) using the 14day modification of the WHO field test.

Results: One hundred and sixty of 196 enrolled patients completed the study. Children in both groups received CQ (25mg/kg) over three days plus CP 6mg (patients <5years) or 8mg stat (>5years) followed by 4mg 8 hourly for 7days. Adults received 1500mg over 3 days in combination with CP, 8mg stat followed by 6mg 8 hourly for 7days. D7 and D14 cure rates were 95.5% and 91.4% in Group 1 versus 87.7% and 77.14% for Group 2 (p=>0.05). Mean PCT and FCT were 2.27±0.84d and 2.56±1.4d versus 2.62±1.36d and 2.7±0.82d in Groups 1 and 2 respectively (p=>0.05). Six patients who earlier failed unsupervised therapy responded to the combination under supervision.

Conclusion: CQ-CP is effective in the treatment of acute uncomplicated falciparum malaria in the community. However, poor compliance may compromise this cheap and effective regimen.

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INTRODUCTION

Falciparum malaria remains a major cause of morbidity and mortality among African children and is most severe among poor rural dwellers[1-2]. Chloroquine, which is cheap, safe and easily available, was the drug of choice Nigeria at the time of this study. Although the national malaria treatment guideline in Nigeria now indicates that artemisinin containing combination therapy is the preferred option[3], chloroquine is still widely used in the country for reasons of high cost and poor availability of ACTs as well as unwillingness of healthcare workers to change from the well known chloroquine to the relatively unknown ACT. However, it is a well recognized fact that the efficacy of chloroquine has been eroded by the development and spread of drug resistance strains of Plasmodium falciparum [3,4]. Some non-antimalaria drugs have been shown to reverse chloroquine resistance in-vitro[5-8], and in in-vivo animal model[9,10]. The clinical application was demonstrated only in 1997 when the combination of chloroquine plus chlorpheniramine (CQ-CP) was shown to be superior to chloroquine alone in the treatment of acute uncomplicated malaria in Nigerian children[9,10]. Since then, the effectiveness and safety of multiple dose chloroquine (CQ) plus chloropheniramine (CP) combination in the treatment of acute uncomplicated falciparum malaria has been well established 1[1-13]. However, all previous studies have been carried out within the hospital setting. Multiple dosage and prolonged regimen of chloropheniramine as well as drowsiness, the most common adverse effect of the combination are important factors that can affect the efficacy of this effective, affordable and safe combination. In this paper, we describe the effectiveness of and compliance with CQ-CP in the treatment of acute uncomplicated malaria in a rural community in Southwestern Nigeria outside the strict confine of the hospital.

PATIENTS AND METHODS

The study was conducted at Olode-Adetoun village in Ona-Ara Local Government Area of Oyo State, of Nigeria between September 1998 and August 2000. Olode-Adetoun is located in the rain forest belt of Nigeria, an area of intense malaria transmission. The inhabitants are peasant farmers who have settled around their farmlands. The University of Ibadan/University College Hospital Joint Ethical Review Committee provided ethical approval for the study. Community consent and support for the studies was obtained from community leaders (village heads, chiefs and women leaders). In addition, verbal informed consent was obtained from each patient' over 18 years of age or from a parent /guardian of patients below 18years of age. Patients aged 6months and above with clinical features compatible symptomatic acute uncomplicated malaria were enrolled into the study.

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Other inclusions criteria included fever (temperature =37.5^{0}C or a history of fever (temprature=37.5^{0}C) or a history of fever within 48 hours preceding presentation, pure *plasmodium falciparum* parasitaemia and a negative history of antimalarial drug administration in the preceding 7 days. Patients with a history of intolerance to chloroquine chlorpheniramine were excluded from the study. Other exclusion criteria were failure to give informed consent or patients on a short-term visit to the community. Patients who were not acutely ill though with patent parasitaemia were not enrolled into the study. In addition, patients who had other illnesses that could affect assessment of treatment outcome such as otitis media, acute respiratory infection or sickle cell anaemia were excluded from the study. Patients were withdrawn from the study if they failed to comply with protocol, had serious adverse event or developed intercurrent infection.

A careful history was taken followed by thorough physical examination of each patient before enrollment. Each patient was subsequently weighed and axillary temperature taken. Thick and thin blood films were prepared from a finger prick and stained with 10% fresh Giemsa stain for parasite identification and quantification. Enrolled patients were randomized into one of the two treatment groups according to a pre-generated randomization table. Patients in group 1 were randomized to receive supervised therapy with chloroquine (25mg/kg body weight) over 3 days plus chlorpheniramine 6mg stat (patients <5yrs of age) or 8mg stat (=5yrs old) followed by 4mg every 8 hours for 7days while those in group 2 received the same dosage of drugs for the respective age groups unsupervised. Adults received 1500mg of chloroquine over 3 days in combination with chlorpheniramine 8mg stat followed by 6mg 8hourly for 7days. A physician or nurse at the village clinic administered the first dose of drugs for all patients at the village clinic. Subsequent doses of drugs were administered by the nurse or village health worker for Group 1 (supervised) patients at the clinic or at home for doses due outside clinic hours. Patients who received unsupervised therapy (group2) had subsequent doses of their drugs dispensed and given to them or to their parent/guardian with instructions on usage. Drugs were administered with ample amount of water and the mouth checked in patients receiving supervised therapy while patients receiving unsupervised therapy were instructed to do the same. Patients in both groups were seen on Days 3,7,&14 while those in group 1(supervised) had additional follow-up on Days 1 and 2 for drug administration. Patients in both groups were followed up for 14 days. All enrolled patients were examined on each visit and blood samples taken for malaria parasite quantification. Patients, parents and guardians were questioned about compliance with therapy and adverse events observed through out the period of drug therapy and follow-up. Additional management included tepid sponging and paracetamol at a dose of 10mg/kg in patients with axillary temperature =38^{0}C. The 14-days modification of the World Health Organization extended field test was used in the study in order to avoid difficulties in differentiating reinfection from recrudescence14. Giemsa stained thick blood films were examined under an oil immersion objective at x 1000 magnification. Parasite density was determined by counting the number of asexual parasites relative to 200 leukocytes in each thick blood film and assuming a mean leukocyte count of 6000/µ1 of blood.

Treatment outcome was based on parasitological cure rates on days 7and 14. Cure rates on days 7 and 14 were defined as the proportion of patients cleared of asexual parasitaemia within the specific time intervals after initiation of treatment without recrudescence within the specified time period. In addition, mean parasite clearance time (PCT), fever clearance time (FCT) and symptom clearance time (SCT) were assessed. Parasite clearance time was defined as the time interval between initiation of drug therapy and clearance of patent parasitaemia, which remained clear for the period of 14days follow up while FCT was defined as time taken from instituting therapy for temperature above 37.5^{0}C to come down to 37.2^{0}C and remain below 37.50C for at least 72 hours. Symptom clearance time on the other hand was defined as the time needed for patients to be free of clinical symptoms related to malaria after instituting therapy. Associated adverse effects of therapy and treatment outcome (Day 7 and D14 cure rates) were compared in the two groups to assess the effectiveness and safety of the combination. Data collected on the patients were analyzed using Epi-info version 6 statistical software15. Proportions were compared by calculating chi-square with Yates proportion or Fishers' exact test. Normally distributed data were compared by Student's test and Kruskal Wallis test. Values are given in the text and tables as mean ±standard deviation and values of $p<0.05$ were taken as significant.

RESULTS

One hundred and sixty of 196 (81.6%) enrolled patients completed the study as stipulated by study protocol. Ninety of these received supervised therapy while therapy in 70 patients was unsupervised. Sixteen of 196 (8.2%) enrolled patients (4 supervised and 12 unsupervised) were lost to follow up because they travelled out of the village to the city for various social events during the study period. Twenty other patients who were all less than 5 years of age were withdrawn as a result of intercurrent disease during the study. Three of these patients had acute respiratory tract infection while the others contracted measles during a measles epidemic, which occurred in the village in year 2000. Fourteen of 16 patients that were lost to follow up, were free of patent parasitaemia and symptoms between Days 3 and 7. Response of malaria to therapy was also prompt in those children who later developed measles during the follow-up period. Clinical and parasitological parameters of enrolled patients are shown in Table 1. Despite the use of pretreatment randomization, parasite density in the patients randomized to receive supervised regimen was significantly higher than in those randomized to receive unsupervised therapy. However, the distribution of other characteristics of the two groups was similar. The clinical picture of malaria was more severe in children who less than five years of age compared to those who were older, with higher initial body temperatures and significantly higher parasite load. Sixteen of 17 patients who had parasite densities above 25,000 asexual parasitesµl (94.12%) were below the age of 5 years. However, the response of the

infection to treatment was not related to the initial parasite load. Two patients (one in each arm of the study) with parasite loads less than 500/µl at enrollment, failed to respond to therapy with the combination while response in patients with much higher parasite loads was good and prompt. Generally, the parasite density in adults was lower than in children (Table1). The therapeutic response of falciparum malaria to CQ-CP in the two groups is presented in Table 2. The overall cure rates on D7 (95.5%) versus 91.4%) and D14 (87.7% versus 77.14%) were higher among patients whose therapy was supervised than those whose therapy was not supervised. Mean FCT was shorter among patients who received supervised therapy (2.27days (±0.84) versus 2.62days (±1.36) than among those whose therapy was unsupervised. Mean PCT was also shorter {2.56days (±1.4)}among patients in group1 compared to patients in group 2 {2.84days (±1.66)}. The differences were however not statistically significant. (P=0.13 and 0.28) (Kruskal Walli's test of significance foe unequally distributed variables.

Patients in whom patent parasitaemia reappeared on or before D14 were re-treated with a single dose of sulphadoxine-pyrimethamine, supervised combination of chloroquine and chlorpheniramine or halofantrine. Patent parasitaemia cleared in all re-treated patients by day 3 and remained cleared up to D14 irrespective of antimalarial drug used for re-treatment. Six of the re-treated patients who failed initial unsupervised therapy were subsequently cured with the same regimen under supervision.

Adverse effects to CQ-CP were few and mild and did not necessitate discontinuation of therapy in any of the enrolled patients. Pruritus and drowsiness were the most common adverse effects reported and these reactions were more common among adults. Six of 27 adults (22.2%); three in each arm complained of drowsiness which was most severe during the first two days of therapy. These patients reported that they were able to resume their regular daily activities by day 2 of treatment. In contrast, only 4(4/133; 3%) parents complained of drowsiness in their children. Pruritus was reported by 4 adults (4/27; 14.8%) and 3 children (3/133; 2.3%) Pruritus was mild in all patients who reported this adverse event and resolved within 5 days without any additional or specific therapy. Antimalaria therapy was not interrupted in any of the enrolled patients on account of adverse event.

Some unused antimalaria drugs were found carelessly thrown around the home of some patients whose therapy was unsupervised during unscheduled home visits. A strip of chlorpheniramine tablet in one case and a tablet of chloroquine plus 4 tablets of chlorpheniramine from another lay in the dirt around the home of another patient. Parents of four children in group 2 reported that their children were unwilling to take drugs at home after clearance of symptoms. Another mother conveniently forgot to continue therapy and traveled out of the village after the child became asymptomatic after D5. Mothers of three other children whose therapy was unsupervised and who were cured admitted to completing only 5days of chlorpheniramine on direct questioning.

Table 1: Clinical Characteristics of Patients with Acute Uncomplicated Malaria Treated with Chloroquine and Chlorpheniramine Combination at Enrollment.

PARAMETER	GROUP 1 SUPERVISED	GROUP 2 UNSUPERVISED
Total No Enrolled	90	70
Total: Sex ratio (M:F)	34:56	30:40
Age (Yrs)		
Mean (± sd)	11.94 (± 14.48)	12.80 (± 15.51)
Range	0.5-62	0.58-70
No. of children age <15yrs	76	57
Sex ratio of children (M:F)	29:47	26:31
No. of adults = 15 yrs	14	13
Sex ratio of adults (M:F)	5.9	4.9
Axillary Temperature (^{0}C) *[Total]*		
Mean (± sd)	37.76 (± 94)	37.87 (± 0.95)
Range	36^{0}C – 39.8^{0}C	36^{0}C-C40.4^{0}C
Axillary Temprature *[children]*		
Mean (sd	37.75^{0}C (± 0.95)	37.87^{0}C (± 0.95)
Range	36^{0}C – 39.8^{0}C	36.5^{0}C – 0.40^{0}C
Axillary Temprature *[Adults]*		
Mean (± sd)	37.16^{0}C (± 0.74)	37.32^{0}C (±0.69)
Range	36.2^{0}C-38.4^{0}C	36.5^{0}C-39.0^{0}C
D0 Parasite density/µl *[children]*		
Mean (± sd)	24,871 (± 75,317)	8,785 (±15,461)
Range	288 – 480,000	249 – 67,789
D0 Parasite density/µl *[adults]*		
Mean (± sd)	659(± 479)	458(± 461)
Range	146-1,800	120-1,650

Table 2: Therapeutic Responses of Patients Suffering from Acute Uncomplicated Malaria Treated with Chloroquine and Chlorpheniramine Combination.

PARAMETER	GROUP 1 (SUPERVISED)	GROUP 2 (UNSUPERVISED)
Total No.	90	70
Children:		
Cure Rate D7	72/76 (94.7%)	53/57 (93%)
Cure Rate D 14	65/76 (85.5%)	44/57 (77.2)
FCT: Mean (± sd)	2.3 (± 1.02)	2.52 (±1.17)
Range (d)	1-5	1-5
SCT: Mean (± sd)	2.3 (± 1.01)	2.37 (± 1.00)
Range (d)	1-5	1-5
PCT: Mean (± sd)	2.58 (± 1.08)	2.87 (± 1.36)
Range (d)	1-5	2-5
Adult:		
Cure Rate D7	14/14 (100%)	11/13 (84.6%)
Cure Rate D14	14/14 (100%)	10/13 (76.9%)
FCT: Mean (± sd)	2.143 (±0.53	3.2 (±2.04)
Range (d)	1-3	1-5
PCT: Mean (± sd)	2.429(± 1.4)	2.7 (± 0.82)
Range (d)	1-5	2-4
SCT: Mean (± sd)	2.00 (± 0.82)	2.16 (± 0.86)
Range (d)	1-3	1-5
Total:		
Cure Rate D7	86/90 (95.5%)	64/70 (91.43%)
Cure Rate D14	79/90 (87.78%)	54/70 (77.14%)
FCT: Mean (± sd)	2.27(± 0.84)*	2.62 (± 1.36)**
Range (d)	1-5	1-5
PCT: Mean (± sd)	2.56 (± 1.13)'''	2.84 (± 1.66) AA
Range (d)	1-5	2-5
SCT: Mean (± sd)	2.28 (± 0.99)$^{+}$	2.5 (± 1.06)++
Range (d)	1-7	1-5
FCT *n==83	**n=66	Kruskal Wallis test P= 0.1383
$PCTA_n$==86	AA_n=64	Kruskal Wallis test P= 0.2776
SCT + n==90	++n=70	Kruskal Wallis test P= 0.1729

DISCUSSION

The use of resistance modulating agents is one of the strategies that can be deployed in overcoming drug resistance in chemotherapy. Chlorpheniramine, a histamine type 1 receptor antagonist is one such resistance-modulating agent, which has been shown to enhance the sensitivity of *P. falciparum* to chloroquine[7,10] thereby prolonging the clinical useful life of this safe and affordable malaria drug. The efficacy of chloroquine plus chlorpheniramine (CQ-CP) against chloroquine sensitive and chloroquine resistance infections in hospital-based studies is well established[11-13]. The results of this study confirm that CQ-CP is effective and safe in the treatment of acute uncomplicated falciparum malaria in the community outside the strict control of a hospital setting. All patients treated showed prompt relief of symptoms within 3 days of starting drug therapy. Cure rates among children who received supervised therapy were higher than those in whom treatment was unsupervised (95.6%, 87.1% versus 91.4% and 77.1%) at D7 and D14 respectively. A D14 cure rate of 77.1% among children from Southwestern Nigeria whose therapy was unsupervised is a significant improvement on D14 cure rates of 47.8% and 50% obtained with chloroquine alone in previous studies from the same area [4,16]. A full course of chlroquine plus chlorpheniramine costs between 40 and 50 cents (USD) and is available in all parts of Nigeria including the rural areas where health care facilities are few and far between. In addition, to improved cure rates, the grade of resistance among patients failing treatment with CQ-CP was milder than previously observed among patients treated with chloroquine alone as only RI and RII pattern of resistance was seen among the patients who failed therapy with the combination. Early and appropriate use of this combination has the potential value of curing patients with acute uncomplicated malaria or at least arresting progression to more severe disease in cases of infection due to partially resistant strains of *plasmodium falciparum*. The addition of sulphadoxine-pyrimethamine on the first day of therapy will most probably improve cure rate remarkably. The result of a sequential therapy of CQ-CP and sulphadoxine-pyrimethamine is a pointer to this expectation[17].

The relative lack of adverse effects apart from drowsiness and pruritus found in this study is consistent with the previous studies on the combination[11-13]. This study is not surprising as chloroquine and chlorpheniramine have along history of good safety profile unlike the newer antimalaria drugs (e.g. mefloquine, halofantrine) which are more expensive, not easily available and often more toxic. However, compliance of this multiple dose regimen was found to be poor when therapy is unsupervised. Cure rates were not only higher among children whose therapy was supervised but also among adults in the same group. Cure rates of 100% were recorded on days 7 and 14 for adults who received supervised therapy in contrast to 84.6% and 76.9% among adults whose therapy was unsupervised. We believe that the lower cure rates among patients in group 2 are a reflection of poor compliance as was observed on occasions during unscheduled home visits when unused drug were found around some homes. This is similar to the poor compliance reported by White et al[18] with drug regimens lasting more than three days among Thai patients whose malaria he was treating with a combination of quinine and tetracycline.

It is noteworthy that two of our study participants, one in each group with parasite density <500/µL failed to respond to therapy with CQ-CP and had to be retreated wit halofantrine to achieve cure on day 7 while patients with higher parasite densities >25,000/µL responded promptly. Although patients with peripheral parasite density of <1000/µL are not usually enrolled in efficacy clinical trials, they however satisfied the inclusion criteria of this effectiveness study.[12]

In conclusion, CQ-CP combination is effective and safe in the treatment of acute uncomplicated malaria in the community. Cure rates of 95% to 98% in hospital studies among children treated with CQ-CP[11-13] were consistently higher than what was obtained in this community study among children (77.2%) using the same dose of CQ and CP Evaluation of a higher dose of CP in a hospital setting led to an increase in the incidence of drowsiness without a corresponding increase in effectiveness or efficacy[19]. The addition of sulphadoxine-pyrimethamine to this combination will markedly improve cure rates and reduce duration of treatment. A reduction in duration of treatment following addition of sulphadoxine-pyrimethamine and improved health education in the community will also go a long way in improving compliance.

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