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POTENTIAL TOXICITY OF CHLORPHENIRAMINE PLUS CHLOROQUINE FOR THE TREATMENT OF CHILDHOOD MALARIA

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ABSTRACT

Objectives: To compare the adverse effects of two regimens of chlorpheniramine plus chloroquine (CP+CQ) in children who live in a country where chloroquine resistant malaria is endemic.

Methods: 99 children with acute uncomplicated malaria were randomised into two treatment groups. Group I received high dose chlorpheniramine (6mg +12mg/day for 7days in children = 5years; 8mg + 18mg/day for 7 days in those >5years) plus chloroquine 10mg/kg daily for 3 days. Group II received a 50% higher dose of chlorpheniramine plus chloroquine 10mg/kg daily for 3 days. Outcome measures were vital signs, clinical response and parasite clearance on days 0-7 and day 14.

Results: Parasite clearance, fever clearance and cure rate were comparable for the two groups. Drowsiness occurred in 66.7% of high dose and 86.3% of higher dose CP+CQ subjects ($p = 0.05$). Compared to children treated with high dose, those treated with higher dose CP+CQ had significantly lower respiratory rates on day 2 ($p = 0.001$), day 6 ($p = 0.015$), and on day 14 ($p = 0.003$).

Conclusion: The higher rates of drowsiness and lower respiratory rates in children treated with higher dose CP+CQ calls for caution in the clinical application of the higher dose combination. The higher dose has no additional benefit and may in fact be dangerous.

Key Words: Chloroquine resistant malaria, chlorpheniramine-chloroquine, treatment, adverse effects, drowsiness, respiratory depression. *(Accepted 15 May 2008)*

INTRODUCTION

Chloroquine resistant malaria remains a major cause of morbidity and mortality in sub Saharan African children[1]. Although the World Health Organisation (WHO) has recommended Artemisin-based Combination therapies (ACTs) as the best anti-malarial drugs currently available[2], the use of ACTs in clinical practice has remained very low due to several limitations including high cost, low public awareness, limited data on safety particularly during pregnancy and insufficient supply relative to demand[3,4]. Given these limitations, the diffusion of the WHO ACT guidelines into routine clinical practice is likely to take many years particularly in poor developing countries where chloroquine remains an important drug in malaria chemotherapy, despite the widespread resistance of *Plasmodium falciparum* to chloroquine[1,5].Given the relatively low cost and ready availability of chloroquine, evaluation of drug combinations that reverse the resistance of *P.falciparum* to chloroquine is being widely explored in order to prolong its "clinical life"[6] for susceptible populations with limited or no access to ACTs. The resistance of *P.falciparum* to chloroquine can be modified and reversed *in vitro* by non-antimalarial drugs including antihistamines (promethazine [7] and chlorpheniramine), calcium channel antagonists (verapamil) and phenothiazines[8]. In-vivo studies also demonstrate the efficacy of chlorpheniramine in reversing chloroquine resistance and preliminary data suggests that this reversal may be dose dependent, with increasing efficacy for reversal demonstrated with higher doses of chlorpheniramine combined with high dose chloroquine therapy[9,10]. However, data is sparse on the clinical adverse effects associated with higher dose chlorpheniramine-chloroquine (CP+CQ) combination therapies, particularly in the pediatric age group. In this study, we examined the adverse clinical effects of high dose chlorpheniramine (6-8 mg stat, then 12-18 mg/day X 7days) versus higher dose chlorpheniramine (9-12 mg stat, then 18-24 mg/day X 7days) in combination with high dose chloroquine (30mg/kg body weight) in a pediatric population in western Africa. The usual therapeutic dose of chloroquine is 25mg/kg body weight and the usual antihistaminic therapeutic dose of chlorpheniramine is

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12mg/day for 3 days. The higher doses of chlorpheniramine used in this study reflect the chloroquine resistance modifying effect of the chlopheniramine, rather than the lower antihistaminic doses of chlorpeniramine, used to treat pruritus associated with chloroquine therapy. We present data on the prevalence of adverse effects of high dose chlorpheniramine combination therapies used to modify chloroquine resistance in Nigerian children diagnosed with acute uncomplicated falciparum malaria.

MATERIALS AND METHODS

The study subjects were selected from pediatric patients attending the General Out Patient Clinic, University College Hospital, Ibadan, Nigeria. The study protocol was approved by the Joint University of Ibadan/University College Hospital Institutional Review Committee. Informed consent was obtained from parents or legal guardians of the children selected for the study.A total of 106 consecutive children aged 9 months to 14 years presenting with acute uncomplicated *P.falciparum* malaria that satisfied the inclusion criteria were enrolled into the study. The inclusion criteria were as follows: fever or history of fever in the 24-48 hours before presentation, clinical symptoms compatible with acute uncomplicated falciparum malaria, pure *Plasmodium falciparum* parasitaemia with parasite density >1000 asexual forms/µl of blood, and absence of concomitant illness such as bronchopneumonia. A detailed medical history was obtained and a standardized physical examination was performed for each subject. Vital signs including pulse rate, respiratory rate, systolic and diastolic blood pressure, were performed. Body weight, height and axillary temperature were also recorded by the same observer. The clinical data were collected with a study-specific Case Record Form. Thick and Thin blood films from finger pricked capillary blood were obtained and Giemsa stained for identification and quantification of malaria parasites. Subjects were randomized to receive one of two treatment regimens, using pre-packed sealed envelopes. Each envelope was opened only after the subject had been recruited into the study. The treatment assignments were as follows: Group I (High dose Chlorpherinamine + Chloroquine): Subjects received chloroquine (30 mg base/kg of body weight) orally as 10 mg/kg daily over 3 days plus chlorpheniramine mealate 6mg orally start dose at presentation, followed by 12mg/day orally in three divided doses every 8 hours for 7 days (days 0-6) if they were 5 years and below. For subjects who were older than 5 years, they received a start dose of 8 mg of chlorpheniramine followed by 18mg/day orally in three divided doses every 8 hours for 7 days (days 0-6) in addition to chloroquine (10 mg/kg daily over 3 days) as described above. Group II (Higher dose Chlorpheniramine + Chloroquine): Patients in this group received chloroquine (30mg base/kg of body weight) orally as 10mg/kg daily over 3 days plus chlorpheniramine 9 mg orally start dose at presentation, followed by 18mg/day orally in three divided doses every 8 hours for 7 days (days 0-6) if they were 5 years and below . For subjects who were older than 5 years, they received a start dose of 12 mg of chlorpheniramine followed by 24mg/day orally in three divided doses every 8 hours for 7 days (days 0-6) in addition to chloroquine (10 mg/kg daily over 3 days) as described above.The chloroquine doses and first daily doses of chlorpheniramine were administered by the study physician and subjects were observed in the clinical unit for at least 3 hours each day. The subsequent daily doses of chlorpheniramine were administered at home by the parents/guardian. Clinical observations were recorded daily from days 0-7 and on day 14 by a single observer who was blinded to the treatment assignments. Vital signs including temperature, pulse rate, blood pressure and respiratory rate, and an assessment of drowsiness/sedation were checked daily at each clinic visit before thick blood films for parasite quantification were performed. The parent/guardian gave information on the drug administration (at home) and adverse effects including drowsiness/sedation, pruritus, and nausea and/or vomiting, abdominal pain and diarrhea at each clinical visit.The fever and parasite clearance times, and cure rates were also determined. Fever clearance time was defined as time from drug administration until the axillary temperature was below 37.5^0C and remained so for at least 72 hours. This definition was necessary because of the routine use of an antipyretic (paracetamol) during the first 36 hours of treatment. The parasite clearance time was defined as the time from drug administration until there was no patent peripheral parasitaemia. The cure rate was defined as the proportion of children who remained free of parasitaemia on day 14 of follow-up[11].

Data and statistical Analysis

Data were analyzed using *Epi-Info version 6* . Data is presented as mean and standard deviation for normally distributed values and are compared using student's t-test. Chi-square with Yate's correction or by Fisher's exact test is used for comparing proportions. Mann-Whitney U test is used to compare skewed data which are presented as median and interquartile range. Differences are deemed to be statistically significant where $p < 0.05$.

RESULTS

Of the 106 subjects enrolled into the study, 99 subjects (93.4%) completed the study. One subject developed severe complicated malaria on Day 0, and as such could not continue in the study while 6 subjects were

lost to follow up. Forty-eight subjects were in Group I (high dose chlorpheniramine + chloroquine), while 51 were in Group II (higher dose chlorpheniramine + chloroquine).

Clinical features at presentation: Table 1 shows the clinical and parasitological characteristics of subjects in the two treatment groups at baseline. There was a higher proportion of females in Group I compared to Group II (68.8% versus 52.9%) although the difference did not achieve statistical significance (p =0.215). The age, weight and vital signs were comparable in the two treatment groups. The mean *P. falciparum* parasite density was similar in the two groups although two subjects in Group I had parasitaemia in excess of 250,000/ul (See Table I).

Therapeutic responses: The mean parasite clearance time was similar in both treatment groups. For Group I (high dose CP+CQ) it was 2.8 0.7 days (range 1-5 days) and for Group II (higher dose CP+CQ), it was 2.9 0.7 days (range 2-4 days) (p=0.58) (Figure 1). Mean fever clearance time was 1.40.7 days (1-3days) and 1.30.7 days (1-4days) for Group I and II respectively (p=0.68) **Figure 2.** The cure rates on day 14 was 95.8% for Group I and 94.1% for Group II (p=0.94).

Clinical adverse effects: Drowsiness/sedation was the most common reported adverse effect of treatment, occurring in 66.7% of Group I (high dose CP+CQ) and 86.3% of Group II (higher dose CP+CQ) subjects (p = 0.05). Pruritus was slightly more common in the higher dose treatment group relative to the high dose group (29.4% versus 22.9%) although it did not achieve statistical significance. Reports of diarrhea, abdominal pain, and, nausea and vomiting were comparable in the two treatment groups (Table 2).Vital signs obtained on clinic visits from days 0-7 and on day 14 showed that the mean pulse rate was similar in both treatment groups (Table 3). However, more patients in Group II had a pulse rate of more than 100/min on days 7 (64%) and 14 (62%) compared to those in Group I, 54% and 59% respectively. Mean systolic and diastolic blood pressure in the two treatment groups were largely comparable, although on day 3, mean systolic blood pressure was slightly higher in Group II relative to Group I (111 mmHg versus 107 mmHg, p = 0.05) See Table 4. The respiratory rate distribution was skewed; hence the median respiratory rate is reported. Table 5 shows that relative to Group I, Group II (higher dose CP+CQ) subjects tended to have lower respiratory rates in response to treatment with statistically significant differences on day 2 (p = 0.001), day 6 (p = 0.015), and on day 14 (p = 0.003).

Table 1 **Clinical and Parasitology Parameters of Children with Acute *P. falciparum* Malaria at Baseline.**

	Group I (High Dose) N = 48	Group Ii (Higher Dose) N = 51	P Value
*Female (%)	68.8	52.9	0.215
Age (years) mean ±sd	6.1 ± 2.9	6.1 ± 3.2	0.98
range	0.8 – 12	1.5 – 13.5	
Weight (kg) mean ±sd	18.0 ± 6.0	17.6 ± 6.4	0.74
range	7.1 - 37	9.5 - 40	
Temp on admission(^{0}C) mean ±sd	38.4 ± 1.1	38.4 ± 1.3	0.99
range	36.4 - 40.7	36.2 - 40.7	
Heart rate (beats/min.) mean ±sd	120 ± 24	121 ± 22	0.87
range	76 -180	76 -172	
Respiratory. Rate (cycles/min)			
mean ±sd	37 ± 11	35 ± 9	0.22
range	20 - 68	16 - 60	
#Median, Interquartile range	32, 10	36, 15.5	0.877
Systolic blood pressure			
mean ±sd	113 ± 14	111 ± 12	0.57
range	70 - 150	80 - 130	
Diastolic blood pressure			
mean ±sd	70 ± 12	65 ± 11	0.54
range	50 - 100	40 - 90	
Parasite density (/ul)			
geometric mean	22,336	17,100	0.26
range	1229-1,846,0002	1,562-211,5530	
No. of Subjects with >250,000/ul			

*Fisher's exact test

#Respiratory rate showed a skewed distribution, the median and interquartile range was reported.High dose CP+CQ: Chlorpheniramine 6-8 mg stat, then 12-18 mg/day X 7days + Chloroquine 10mg base/kg X 3days

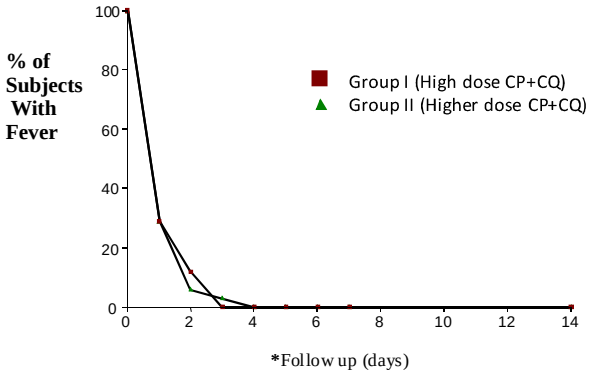
Higher dose CP+CQ: Chlorpheniramine 8-12 mg stat, then 18-24 mg/day X 7days + Chloroquine 10mg base/kg X 3days

Table 2: **Adverse effects of two treatment regimens of chlorpheniramine plus chloroquine (CP+CQ) in children with acute *P. falciparum* malaria.**

	Group I (High Dose CP+CQ) N = 48	Group II (Higher Dose CP+CQ) N = 51	P value
Drowsiness	32 (66.7%)	44 (86.3%)	0.05
Pruritus	11 (22.9%)	15 (29.4%)	0.64
Diarrhea	5 (10.4%)	6 (11.8%)	1.0
Abdominal pain	4 (8.3%)	4 (7.8%)	1.0
Nausea and vomiting	3 (6.3%)	3 (5.9%)	0.71

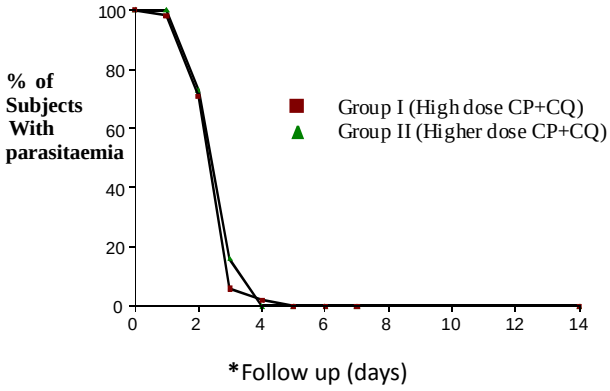
High dose CP+CQ: Chlorpheniramine 6-8 mg stat, then 12-18 mg/day X 7days + Chloroquine 10mg base/kg X 3days
Higher dose CP+CQ: Chlorpheniramine 8-12 mg stat, then 18-24 mg/day X 7days + Chloroquine 10mg base/kg X 3days

Figure 1: **Rate of Fever Clearance in Children with Acute *P. Falciparum* Malaria Treated With Two Regimens of Chlorpheniramine Plus Chloroquine (CP+CQ)**



*Clinical observations on days 0-7 and on day 14.
High dose CP+CQ: Chlorpheniramine 6-8 mg stat, then 12-18 mg/day X 7days + Chloroquine 10mg base/kg X 3days
Higher dose CP+CQ: Chlorpheniramine 8-12 mg stat, then 18-24 mg/day X 7days + Chloroquine 10mg base/kg X 3days.

Figure 2: **Rate of Parasite Clearance in Children with Acute *P. Falciparum* Malaria Treated With Two Regimens of Chlorpheniramine Plus Chloroquine (CP+CQ).**



*Clinical observations on days 0-7 and on day 14.
High dose CP+CQ: Chlorpheniramine 6-8 mg stat, then 12-18 mg/day X 7days + Chloroquine 10mg base/kg X 3days
Higher dose CP+CQ: Chlorpheniramine 8-12 mg stat, then 18-24 mg/day X 7days + Chloroquine 10mg base/kg X 3days

Table 3: **Pulse Rate in Children with Acute *P. Falciparum* Malaria Treated With Two Regimens of Chlorpheniramine Plus Chloroquine (CP+CQ).**

Pulse rate beats/min.)	Group I (High Dose CP+CQ) N = 48			Group II (Higher Dose CP+CQ) N = 51			p value
	Range	Mean	sd	Range	Mean	sd	
Day 0	76-180	120	24	76-172	121	22	0.87
Day 1	76-144	107	17	84-176	114	20	0.07
Day 2	72-152	105	19	68-168	108	22	0.51
Day 3	72-148	101	16	76-140	102	15	0.77
Day 4	76-136	100	15	68-152	102	17	0.56
Day 5	72-112	93	17	68-112	92	17	0.78
Day 6	68-144	91	26	72-124	101	18	0.19
Day 7	68-140	103	16	68-140	104	15	0.75
Day 14	72-120	100	13	64-152	103	19	0.53

High dose CP+CQ: Chlorpheniramine 6-8 mg stat, then 12-18 mg/day X 7days + Chloroquine 10mg base/kg X 3days
Higher dose CP+CQ: Chlorpheniramine 8-12 mg stat, then 18-24 mg/day X 7days + Chloroquine 10mg base/kg X 3days.

Table 4: **Systolic and Diastolic Blood Pressure in Children with Acute *P. Falciparum* Malaria Treated With Two Regimens of Chlorpheniramine Plus Chloroquine (CP+CQ)**

*Blood Pressure (mmHg)		Group I (High Dose CP+CQ) N = 48			Group II (Higher Dose CP+CQ) N = 51			p value
		Range	Mean	sd	Range	Mean	sd	
Day 0	Systolic	70-150	113	14	80-130	111	12	0.57
	Diastolic	50-100	70	12	40-90	65	11	0.54
Day 1	Systolic	90-140	111	11	80-140	111	14	0.72
	Diastolic	40-90	68	11	40-90	70	12	0.55
Day 2	Systolic	90-130	110	12	80-140	111	11	0.51
	Diastolic	40-100	67	13	50-90	68	9	0.70
Day 3	Systolic	80-130	107	12	90-150	111	11	0.05
	Diastolic	40-90	67	11	50-100	69	11	0.23
Day 7	Systolic	70-130	110	12	90-130	111	11	0.51
	Diastolic	50-90	67	11	50-90	67	11	0.80
Day 14	Systolic	70-130	106	13	90-130	111	12	0.06
	Diastolic	50-80	63		40-80	65	9	0.61

*All blood pressure measurements were taken in the supine position; mmHg millimeters of mercury.
High dose CP+CQ: Chlorpheniramine 6-8 mg stat, then 12-18 mg/day X 7days + Chloroquine 10mg base/kg X 3days
Higher dose CP+CQ: Chlorpheniramine 8-12 mg stat, then 18-24 mg/day X 7days + Chloroquine 10mg base/kg X 3days

Table 5: **Respiratory Rate in Children with Acute *P. Falciparum* Malaria Treated With Two Regimens of Chlorpheniramine Plus Chloroquine (CP+CQ).**

Median respiratory rate/minute	Group I (High Dose CP+CQ)	Group II (Higher Dose CP+CQ)	*p value
	N = 48	N = 51	
Day 0	32	36	0.88
Day 1	32	28	0.28
Day 2	32	28	0.001
Day 3	32	28	0.09
Day 4	28	28	0.34
Day 5	32	28	0.27
Day 6	31	25	0.015
Day 7	28	28	0.09
Day 14	29	24	0.003

*Mann-Whitney U test

High dose CP+CQ: Chlorpheniramine 6-8 mg stat, then 12-18 mg/day X 7days + Chloroquine 10mg base/kg X 3days

Higher dose CP+CQ: Chlorpheniramine 8-12 mg stat, then 18-24 mg/day X 7days + Chloroquine 10mg base/kg X 3days.

DISCUSSION

In this study, we compared the clinical adverse effects of two dose combinations of chlorpheniramine and chloroquine. The indices of therapeutic responses, parasite and fever clearance times in children enrolled in the study were similar in both treatment groups. This suggests that the higher dose CP+CQ had no therapeutic advantage over high dose CP+CQ in malaria cure rates in our study population. However, the persistent tachycardia on days 7 and 14 and slightly elevated systolic blood pressure on day 3 which is more with the higher dose group may suggest cardiac toxicity of the combination or of chlorpheniramine alone. There is also the possibility of other febrile illnesses which may be setting in at this time. The most important finding in this study was significantly lower respiratory rates in the higher dose CP+CQ group relative to the high dose group. The lower respiratory rates were present on several days of treatment and extended beyond treatment, persisting even on day 14 (p=0.003). Abnormalities in respiratory rate and pattern are common clinical manifestations of malaria and/or acute respiratory tract infection, both of which are major causes of childhood morbidity and mortality in sub Saharan Africa. Appropriate management depends on accurate assessment which for most children is based on clinical signs alone. Abnormal respiratory pattern has been reported in severe malaria[12] and is often associated with poor prognosis[13.] Hypoventilation in malaria has been suggested to be either drug-related particularly when diazepam is administered prior to anti-malarial therapy or due to subtle seizure activities[12]. None of the subjects in this study had complicated malaria. In addition, the lower respiratory rate observed during the course of treatment in the higher dose CP+CQ group was not present at presentation but was observed on day 2 after the initiation of CP + CQ combination therapy. Therefore, the lower respiratory rates in Group II subjects may be attributable to the higher dose of chlopheniramine (9-12 mg stat, then 18-24 mg/day X 7days) used in this study. The most common reported clinical adverse event in this study was drowsiness/sedation. This occurred more frequently in the higher dose CP+CQ group relative to the high dose group (86.3% vs. 66.7%; p = 0.05). While this may be an advantage in agitated patients, it may mask symptoms of central nervous system deterioration including mild seizure episodes in complicated malaria. The parasitaemia counts of over one million per microlitre of blood seen in this study are not uncommon in endemic areas and may not necessarily indicate severity of infection[14]. Pruritus was common in the two treatment groups and its occurrence was slightly higher in the higher dose CP+CQ group relative to the high dose CP+CQ group (29.4% vs. 22.9%; p=0.64). This finding suggests a lack of efficacy of higher doses of anti-histamines in the treatment of chloroquine-induced pruritus. The reversal of drug resistance in P.falciparum malaria using chloroquine combinations with medications such as antihistamines[7], calcium channel antagonists and phenothiazines[8] may have potential toxic effects on the host cells. For example, the combination of high doses of chloroquine and verapamil has been reported to result in the death of well differentiated normal human cells, although the cells survived the same concentration of either drug alone[15] . The lower respiratory rates and higher rates of sedation in children treated with higher dose CP+CQ in this study calls for caution in the administration of high dose drug combinations for malaria therapy in children. In the vast majority of sub Saharan Africa hospitals where state-of-the-art diagnostic facilities are extremely limited, clinical signs may provide the only indication of adverse effects of drug therapy. This underscores the need for clinical assessment and close observation of vital signs particularly for pediatric patients.

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