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Research Article

Comparative Cardiac Effects of Chlorproguanil/Dapsone and Chloroquine during Treatment of Acute Uncomplicated Falciparum Malaria Infection in Nigerian Children

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ABSTRACT: Cardiac toxicity has been reported with a number of antimalarial drugs. In this study we compared the cardiac effects of chlorproguanil/dapsone (CD) a new antimalarial drug, with that of chloroquine (CQ) during treatment of acute uncomplicated malaria in Nigeria. We monitored 62children with symptomatic malaria over 14 days by Clinical and electrocardiographic parameters. Thirty-one each received supervised dosing CD (daily for 3 days) or CQ (daily for 3 days). Clinical monitoring was done daily for 8 days and on day 14. Electrocardiographic monitoring was at 0hr, 4hrs, 24hrs, 30hrs, 48hrs, 54hrs, 72hrs, 96hrs, 120hrs, 144hrs, D7 and D14. Sinus tachycardia was the most often observed electrocardiographic abnormality pretreatment. Seven of twenty-eight (25%) children treated with CD in whom pre-treatment Q-Tc intervals were normal had lengthening of Q-Tc interval while 33.3% (9/27) of those treated with CQ had lengthening of Q-Tc interval. ($P< 0.004$, χ^2 test). Post-treatment Q-Tc interval prolongation was observed in 52% and 47.8% of children treated with CD and CQ respectively. Two patients who received CD recorded abnormally prolonged P-R interval (6.5%, $P < 0.025$; χ^2 test). One of the two patients developed primary A-V block between 96 hr and 168 hr. The second patient had occasional ventricular ectopic complexes at 54 hrs, 72 hrs and 96 hrs. There were no clinical symptoms in all the patients. The occurrence of rhythm disturbance in two of the patients who received CD may be pointers to possible cardiotoxic potentials of CD.

Keywords: Chlorproguanil-dapsone, Cardiac effects, falciparum malaria, children.

INTRODUCTION

The emergence of chloroquine- and sulfadoxine-pyrimethamine (SP)-resistant *Plasmodium falciparum* has necessitated the use of alternative antimalarial drugs. Unfortunately, these new drugs are not only more expensive, but are sometimes more toxic than chloroquine and pyrimethamine/sulphadoxine which are first and second line drugs respectively in many national malarial control programmes in sub-Saharan Africa. A prominent adverse event which has been reported with antimalarial drugs is cardiotoxicity. (Kofi-Ekwe 1983, Castot & Rappoport 1993, Monlun *et al* 1993a, 1993b, Sowunmi *et al* 1998). Drugs, which have been found to have significant cardiac effects include, chloroquine, halofantrine, artemisinin derivatives, quinine and quinidine, mefloquine and sulphadoxine/pyrimethamine. (Olatunde 1970, Nosten *et al* 1993, Kofi-Ekwe 1983, Castot & Rappoport 1993, Monlun *et al* 1993a, 1993b, Hien *et al* 1996, Sowunmi *et al* 1998).

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Chlorproguanil/dapsone (CD) a combination of two antifolate drugs with rapid elimination times has been evaluated as a possible replacement for chloroquine and sulphadoxine-pyrimethamine which were the first and second line antimalarial drugs in Africa. The similar short half-lives of both drugs confer an advantage as a substitute antimalarial drug in CQ and SP resistant falciparum malaria. *(*Watkins *et al, 1987;* Ahmad & Rogers 1980*)*. We conducted a prospective study to evaluate the cardiac effects of chlorproguanil/dapsone (CD) and chloroquine (CQ) in Nigerian children with acute symptomatic uncomplicated *falciparum* malarial by clinical and electrocardiographic monitoring at specific interval over a period of 14 days.

PATIENTS AND METHODS:

Patients

The study was conducted between May 2000 and September 2000. Children who were enrolled in a larger study evaluating the safety and efficacy of Chlorproguanil-dapsone (CD), versus sulfadoxine-pyrimethamine (Alloueche *et al* 2004) constituted the CD arm of the study while children in a parallel study evaluating the efficacy of CQ in children suffering from acute symptomatic uncomplicated *falciparum* malaria constituted the CQ arm of the study. The Joint University of Ibadan/University College Hospital Ethics Review Committee provided ethical approval for the study before its commencement.

The cardiac effects of CD and CQ were compared in 62 children aged 12 months to 10 years with symptoms compatible with acute uncomplicated falciparum malaria. Children were enrolled into the study if the following criteria were met: fever or history of fever in the 24 – 48 hrs preceding presentation, pure *Plasmodium falciparum* asexual parasitemia greater than 2000 but less than 100,000/μL of blood, no history suggestive of previous cardiac disorder and signed informed consent of the parent or guardian. Children with a history of intake of any potentially cardiotoxic drug within 1 month of presentation, history of convulsions in present illness, history of antimalarial drug administration in the 2 weeks preceding presentation were excluded from the study. Other exclusion criteria include features of severe or complicated malaria *(Warell et al 1990*), G-6-P-D deficiency and any concomitant disease that may interfere with evaluation of results.

Methods

Prior to enrollment, each child had a thorough history taken and physical examination carried out. Special attention was paid to history suggestive of heart disease and drug intake. Thick and thin blood smears were prepared for parasite identification and quantification. Venous blood samples were taken for hematological and biochemical evaluation of renal and liver functions. A pre-treatment 12-lead electrocardiogram (ECG) was obtained at 25 mm/s paper speed and 10mm/mV sensitivity using a MAC-PC-A3 (Marquette electronics inc.) electrocardiographic machine. Enrolled children received either CD (LapDap™ GlaxoSmithKline) at 2.0 – 2.5mg/kg daily for three days or CQ (Nivaquine™ May and Baker) at a dose of 25 mg/kg over three days in 10 mg/kg D0-D1 and 5 mg/kg on D2. All doses of drugs were administered orally in a supervised regimen. Patients were observed in the clinic for 2 hours to ensure that the drug was retained. If there was vomiting within 30 minutes of drug ingestion, drug administration was repeated. Clinical assessment of pulse, temperature, blood pressure, breath sounds and heart sounds were carried out at every clinic visit. Parents/guardians as well as children who could volunteer information were questioned and examined for presence of adverse drug effects. In addition, thick blood smears were prepared for detection and quantification of malaria parasites, daily for 7 days and then on Day 14. Response of infection to treatment was evaluated using the WHO 1990 criteria.

Follow up electrocardiographic tracings were recorded for both treatment groups at 4 hrs, 24 hrs, 30 hrs, 48 hrs, 54 hrs, 72 hrs, 96 hrs, 120 hrs, 144 hrs, and 168 hrs (D7) and 336 hrs (D14). Electrocardiographic measurements of the ventricular rate, P-R interval, QT and Q-Tc intervals and rhythm were recorded at each evaluation time. These parameters were crosschecked by an independent observer (OOO). The reference lead for measurement of the P-R interval was lead II for all patients. The Q-T interval was measured from the onset of the QRS complex to the end of the T-wave. The end of T-wave was defined as the return of the T-wave to baseline. The Q-T interval was measured in the lead showing the longest interval and was corrected for heart rate Q-Tc) according to Bazett's Formulae *(Bazett – 1920).* The U-wave was not included in the QT measurement *(Park & Guntheroth 1992).* A QTc interval was considered to be significantly prolonged if it was greater than 125% of the baseline measurement or greater than 0.44s *(Garson 1983*).

Statistical analysis:

Data obtained was entered into a computer and analyzed using Epi info version 6 and Prism statistical package (CDC, & WHO 1994). Electrocardiographic intervals) are expressed in seconds as means ± SD and ρ values <0.05 were taken as significant. Comparison

between ECG values at specified time intervals with baseline value was assessed using the paired student T-test and χ^2 test with Yates correction.

RESULTS

Demographic characteristics: Sixty-two children were evaluated (31 CD, 31 CQ) between May 2000 and September 2000. The mean age of children who were treated with CD was 5.8 ± 2.7 years, while that of those who received chloroquine was 5.5 ± 2.7 years. Details of the enrollment characteristics are described in Table I. *Plasmodium falciparum* was the only specie identified in all study participants.

Response of infection to therapy: Fifty-eight (93.6%) of enrolled patients were available for evaluation on D14. All thirty-one who received CD were available for review on D14 while 4 of children who received CQ were lost to follow-up between D7 and D14. All the 4 patients were free of patent parasitaemia when they were last seen. Cure rates at D-7 and D-14 were 100% and 93.5% (29/31) among patients treated with CD, while cure rates at D-7 and D-14 among patients treated with CQ were 87.1% (27/31) and 70.9% (22/31). The differences in D-7 and D-14 cure rates between CD and CQ were statistically significant. (D-7 $\rho<0.02$, D-14 $P<0.05$ χ^2-test). However, there was no statistically significant difference in parasite and fever clearance times between the two groups. [(PCT- P > 0.5)(FCT- P > 0.5) T-test] Tables 1-2.

Clinical Tolerance: Both study drugs were well tolerated. No patient was withdrawn as a result of recurrent vomiting. There were no clinical symptoms of cardiac intolerance to either drug regimen as evidenced by direct response to questioning and clinical examination. There was no significant change in blood pressure during treatment and at follow-up. Mean pre-enrollment hematocrit was 33% in patients that received Chlorproguanil/dapsone and 30.6% among those that received chloroquine. Patients who received CD had a steeper drop in their haematocrit at D7 compared with those who were treated with CQ (ρ = 0.003). Biochemical tests showed only mild increases in alanine aminotransferase enzyme in two of the study patients treated with CD.

ECG findings: : Sinus tachycardia was the commonest electrocardiographic finding which occurred in 54.8% (34/62) of children enrolled into the study (Fig. 1) Fifteen (48.4%) of these patients received CD, while 19 (61.3%) received CQ. There was a positive correlation between heart rate and the presenting body temperature but not with peripheral parasite density. Pre-enrollment P-R interval was normal in all study participants. (Fig, 2). However a P-R prolongation of > 0.180s was observed in 2 of the children that received CD at 96 hrs, 120 hrs, 144 hrs, and 168 hrs. One of the two patients had occasional ventricular ectopic complexes after 4 hrs of drug administration which became more frequent at 54 hrs and 72 hrs returning to normal by 168 hrs (D7) [Figure 3]. Another patient had significant first degree atrio-ventricular (1^0 A-V) block at 96 hrs, 120 hrs, 144 hrs, 168 hrs (D7), returning to normal at 336 hrs (Figure 4).These two children had normal pre-treatment ECG tracings.

Table 1:
Enrolment parameters of children with acute uncomplicated *plasmodium falciparum* malaria treated with Chlorproguanil/dapsone or chloroquine.

CHARACTERISTIC	DRUG TREATMENT	
	Chlorproguanil/ dapsone	**Chloroquine**
Male: Female	13: 18	17: 14
Mean Age (yrs) mean ± sd Range	5.8 ± 2.7 2 - 10	5.5 ± 2.7 1 – 10
Weight (kg) mean ± sd Range	17.8 ± 5.8 10 - 28.5	16.5 ± 6.6 8 – 30
Duration of illness (d) mean ± sd Range	3.2 ±1.4 2 - 6	2.9 ± 1.2 2 – 6
Temperature (^{0}C) mean ± sd Range	38.1±1.0 36.2 – 39.9	38.2 ± 0.8 36.8– 40.5
Parasite density (/μL) GMPD Range	42,503 3120 - 100320	29,554 2014-100500
Haematocrit (%) mean ± sd Range	33.6±14.5 25 - 40	30.6 ±5.8 20 – 39

GMPD = geometric mean parasite density.

Table 2:
Therapeutic response of children with acute uncomplicated falciparum malaria treated with Chlorproguanil/dapsone or Chloroquine.

Characteristics.	Chlorproguanil/dapsone		Chloroquine	
	Mean ±sd	Range	Mean ±sd	Range
Fever clearance time (days)	2.5 ±1.4***	2-5	2.3±1.1***	2-5
Parasite clearance time (days)	4.0 ± 0.7***	3-5	4.2±0.8***	3-5
Cure rates (%) D-7	100%*		87.1%*	
Cure rate (%) D14	93.5%**		70.9%**	

P* = 0.02; P** = 0.05; P*** >0.5.

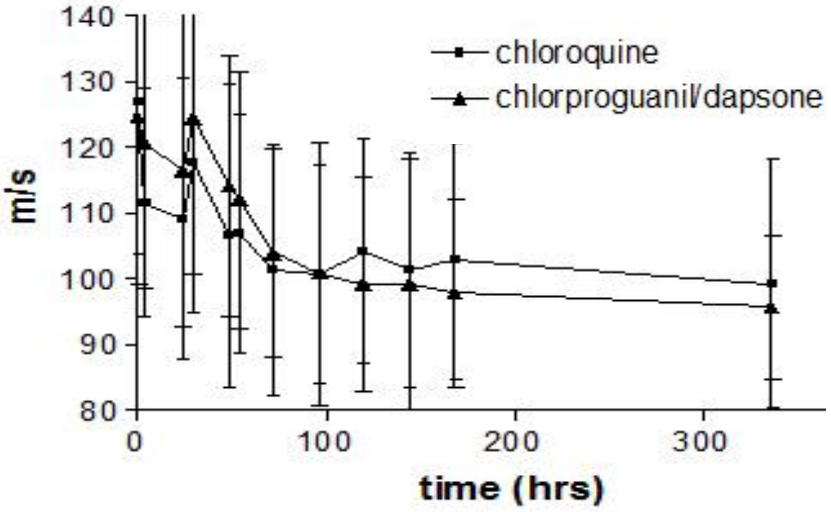

Fig. 1
Marked tachycardia (increased heart rate) at enrollment followed by gradual return to normal to normal by 72 hours

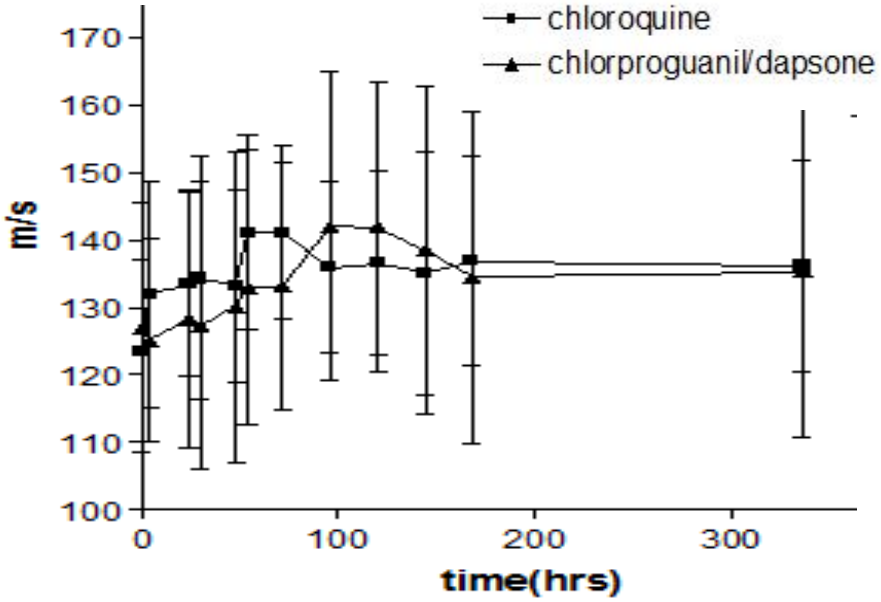

Fig. 2
Pre-enrollment PR-interval within normal limits in study participants with subsequent widening after drug administration in both study groups

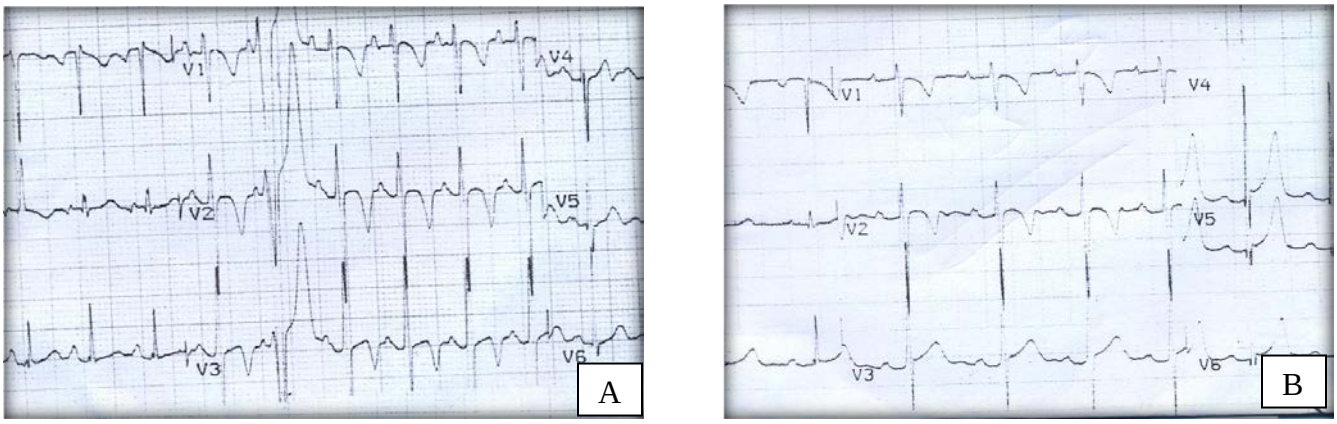

Fig. 3
ECG tracing of the study participant who received LapDap A=-normal ECG at enrollment. B = ECG at 72hours showing multiple ventricular ectopics

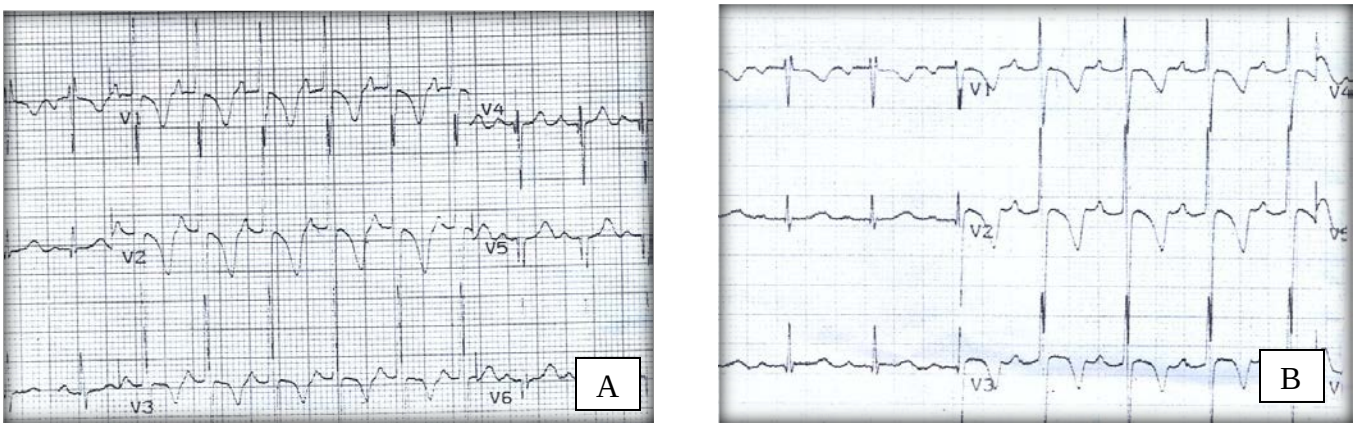

Fig. 4
ECG tracing of one of the study participants who received LapDap . A =. Normal ECG tracing at enrollment; B-= ECG tracing at 120 hours showing 1st degree heart block

Pre-treatment Q-Tc interval prolongation > 0.44s was observed in 11.2% (7/62) of all the children (3-CD, 4-CQ). Further prolongation of the QTc intervals beyond 0.44s was observed in four of the seven children (2-CD, 2-CQ). Eight of 28 (28.6%) of children with normal pre-treatment QTc interval treated with CQ had lengthening of the QTc interval while 25% (7/28) of CD treated children with normal pre-treatment Q-Tc interval recorded lengthening of Q-Tc interval. When compared with pre-treatment values, Q-Tc interval was significantly lengthened at 4 hrs, 24 hrs, 30 hrs, 48 hrs and 54 hrs among 47.8%, 24.1%, 52%, 25%, and 45.2% of children treated with CQ, while 15.4%, 15.4%, 10.7%, 10.3%, and 14.3% of children treated with CD recorded similar observations. Prolongation of the Q-Tc interval was significantly less frequent among children treated with chlorproguanil/dapsone than those with chloroquine. ($P< 0.004$, χ^2 test). There was no incidence of overt clinical intolerance or symptoms suggestive of cardiac malfunction in these patients throughout the period of treatment and follow-up.

DISCUSSION

Sinus tachycardia was the most common pre-treatment ECG finding, which occurred in 54.8% of the patients studied. A positive correlation was observed between tachycardia and level of pyrexia. This is not surprising as fever which is a common clinical feature of malaria in children, is frequently accompanied with sinus tachycardia. A pre-treatment QTc interval prolongation was observed in 11.3% (7/62) of the children. Four of the seven children (2 CD, 2 CQ) had further increases

in the QTc interval prolongation during treatment with both drugs. However there were no symptoms referable to the cardiovascular system. Similar pre-treatment Q-Tc interval prolongation had been reported by previous workers from the same environment (Sowunmi, *et al*. 1999). Asymptomatic familial prolonged QTc interval has also been described after several episodes of convulsions *(Castot et al 1993*). Although children with a history of convulsions in present illness were excluded in this study, previous episodes of convulsions were not considered as exclusion criteria. The few cases of pre-treatment QTc interval prolongation observed in this study may be a result of familial predisposition.

P-R interval prolongation, and a significant A-V block were recorded in two children treated with chlorproguanil/dapsone whereas no such observations were made among the children who received chloroquine during this study. This finding is at variance with previous report of P-R prolongation in 1 of 10 patients after 24 hrs of receiving chloroquine for acute uncomplicated malaria (*Sowunmi et al 1999).* Other antimalarial drugs, notably halofantrine, have also been associated with short duration A-V block in children and dose related lengthening of P-R interval and QTc interval prolongation in adults (*Nosten et al 1993, Sowunmi et al 1999*). Thus the occurrence of P-R interval prolongation is not peculiar to CD alone.

During this study, the proportion of children with QTc interval prolongation > 0.44s at various time points was higher among those who received CQ than those treated with CD (52% versus 47.2%). The difference was however not statistically significant. This agrees with the report of Sowunmi *et al* 1999 in which 50% of children treated with chloroquine had QTc interval prolongation after 48 hrs of therapy. However, we do not have previous study of CD to use as a reference point. Significant QTc interval prolongation between 8 hrs and 48 hrs after treatment with halofantrine was seen in 26% - 68% of patients. This is of short duration in children, unlike adults where a dose related prolongation lasted for more than one week *(Sowunmi et al 1999, Nosten et al 1993).*

Chloroquine has been known to cause prolonged Q-Tc interval and diminution of T-wave, which is dose dependent. *(Bustos et al 1994)* When compared with CD the Q-Tc interval prolongation is of a short duration. This is not unconnected with the mean elimination half-life of CD, which is about 20 – 30hrs. The relatively lower incidence of Q-Tc interval prolongation among children treated with CD (25%) compared with 33.3% of CQ seem to suggest that CD has less cardiotoxic effects than CQ. It is of note that CQ has been used for over 6 decades and its safety especially following oral therapy is legendary. However, there are reports of symptomatic and sometimes fatal cardiovascular adverse events following parenteral therapy with accompanying rapid absorption into the systemic circulation. Although there were no symptoms referable to the cardiovascular system, the P-R interval prolongation and rhythm abnormalities seen in 2 patients [6.5%] ($P < 0.025$, χ^2 test) cannot be ignored. This suggests that CD may produce serious cardiac adverse effects even at therapeutic doses. The 1^0 A-V block observed in one of the study participants which resolved before day 14 post treatment could be due to individual idiosyncrasy or a direct effect of chlorproguanil/dapsone on the heart. Measurement of the pharmacokinetic disposition of CD to establish the relationship between Q-Tc interval changes and plasma drug concentration will be useful in elucidating this.

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