COMPARISON OF CHLOROQUINE WITH QUINIMAX® IN THE TREATMENT OF CEREBRAL MALARIA IN GHANAIAN CHILDREN

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SUMMARY

Despite earlier reports of R2 and R3 resistance of *Plasmodium falciparum* to chloroquine, it remained the drug of choice for the treatment of cerebral malaria in Ghana. The World Health Organisation however recommends the use of parenteral quinine salts in such circumstances.

In order to guide local treatment policies, an open randomised trial comparing the efficacy of enteral chloroquine and intravenous followed by oral Quinimax®, a quinine preparation approved by the World Health Organisation, was conducted in 70 children with cerebral malaria. The primary end points were mortality, prevalence of residual neurologic sequelae and treatment failure (clinical and parasitological).

Thirty-three patients received chloroquine and 37 received Quinimax®. There was no significant difference in mortality rates (chloroquine, 12.1 %; Quinimax®, 10.8%; p=1.00) and neurologic sequelae on day 7 (chloroquine, 12.1%; Quinimax®, 8.1%; p=0.70) . There was a significantly higher prevalence of early treatment failure in the chloroquine group (chloroquine, 12.1%; Quinimax®, 0%; p=0.045). Significantly more patients on chloroquine were parasitaemic on day 3 (chloroquine, 21.8%; Quinimax®, 2.7%; p=0.022) but times to parasite clearance, fever clearance and recovery of full consciousness were similar.

We conclude that treatment failure is more likely when chloroquine is used to treat cerebral malaria than when Quinimax® is used. We therefore recommend that quinine salts, or other antimalarial drugs of equal efficacy be used to treat cerebral malaria in Ghanaian children instead of chloroquine.

Keywords: chloroquine, Quinimax®, quinine, cerebral malaria, children

INTRODUCTION

Plasmodium falciparum malaria continues to be one of the main causes of mortality among children in sub–Saharan Africa[1]. Cerebral malaria (CM) accounts for many of these deaths and is responsible for about 60% of malaria related deaths in children admitted to the Korle Bu Teaching Hospital (KBTH) (Goka *et al,* unpublished data), with a case fatality rate of 15.3%[2]. The emergence of chloroquine resistance in an endemic area has been shown to increase malaria associated mortality among children[3]. I*n vivo* resistance to chloroquine was first reported in Ghana in 1986[4]. This was followed by reports of R1 and R2 between 1987 and 1994[5-8]. R3 resistance was subsequently documented in children with CM in 1997[2] at the KBTH, and also reported among children in the Volta Region (Koram *et al,* unpublished data). Chloroquine has however remained the drug of first choice in the treatment of all forms of malaria in Ghana[9], despite these reports of clinical and parasitological failure. The World Health Organisation (WHO) recommends artemisinin derivatives or parenteral quinine, which have been shown to be equally efficacious, for the treatment of severe *P. falciparum* disease in areas with chloroquine resistant strains[10]. A study conducted in KBTH in 1998 comparing chlororquine and artesunate in the treatment of CM showed a similar outcome for

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patients treated with either drug[11]. Quinimax® (Sanofi -Synthelabo, Gentilly, France) is one of the WHO approved quinine preparations, used mainly in French-speaking West Africa[12], which has recently been registered for use as an antimalarial drug in Ghana. It consists of 96% quinine base, 2.6% quinidine base plus 0.7% each of cinchonidine and cinchonine bases. We conducted this study to compare chloroquine with Quinimax® in the treatment of CM with a view to making recommendations for treatment guidelines.

METHODS

The study was approved by the Ethical and Protocol Review Committee of the University of Ghana Medical School.

Study Design

This was an open randomised comparison of chloroquine by enteral route and Quinimax® initially by intravenous infusion then by oral route in the treatment of CM in Ghanaian children.

The study was conducted in the Department of Child Health, KBTH in July and August 1999 and 2000 during the peak malaria transmission season. Patients admitted with a diagnosis of CM were enrolled consecutively after obtaining written informed parental consent. Each patient was assessed by a project physician. Clinical information was documented by means of standardised forms. Information included duration of symptoms prior to admission and drug history. The Blantyre coma score[13] (BCS) and axillary temperature were documented on admission. The temperature was monitored 4 hourly and BCS twice daily until it normalised (i.e. BCS = 5). The pulse and respiratory rates were monitored 4 hourly for all patients. The pulse rate was monitored hourly when Quinimax® was being infused. Continuous ECG monitoring was not available. The presence of neurological deficits was documented on days 7 and 14.

Inclusion criteria were asexual *P. falciparum* parasitaemia, unarousable coma (BCS 3)[10,13] and duration of coma for 60 minutes following a convulsion. Exclusion criteria were treatment with 20mg/kg chloroquine or any amount of quinine prior to admission; other causes of coma such as head injury or meningitis; pre-existing neurological disease; BCS > 3 immediately after correcting hypoglycaemia; other infection; severe dehydration or shock defined as cold clammy skin with weak radial pulse and systolic blood pressure < 90 mm Hg.

The primary endpoints of the study were mortality and residual neurologic sequelae on days 7 and 14 after the onset of treatment, and treatment failure rate over a 14 day follow up period. Treatment failure was defined by 2 WHO classification systems for response to antimalarial drugs as follows: clinical response - early treatment failure (ETF) or late treatment failure (LTF)[14]; parasitological response - resistance at R1, R2 or R3 levels[15]. The secondary endpoints were the times for fever to decline, to regain full consciousness and for parasites to clear; and prevalence of parasitaemia on day 3. The time intervals were defined as follows: time for fever to settle – interval between onset of treatment and the first time that axillary temperature falls to and remains below 37.5^0 C for at least 48 hours; time to regain full consciousness - interval between onset of treatment and the first time that the BCS = 5 and remains so; time to clear parasites – interval between onset of treatment and the first time that 2 consecutive 12-hourly blood films are negative for *P. falciparum trophozoites*.

Laboratory Investigations

Venous blood was collected for full haematology (automated haematology analyser- Kx-21Sysmex, Japan), Giemsa-stained thick and thin blood films for identification and quantification of asexual forms of *P. falciparum*, random blood sugar, urea and electrolytes. Blood film was repeated twice daily till there were no parasites on 2 consecutive occasions, and then on days 7 and 14. Capillary blood glucose level was monitored 4 hourly until patients were fully conscious, or whenever clinically indicated, using BM-Test® 1-44 strips (Boehringer Mannheim Diagnostics, Germany) and reading against the colour chart on the container. Lumbar puncture was done for cerebrospinal fluid examination to exclude meningitis (normal biochemistry, cell count ≤ 10 lymphocytes /mm^3), when the level of consciousness had improved to Blantyre coma score 4 or 5.

Antimalarial treatment

Antimalarial treatment was started as soon as the venous sample was taken. Children were randomly assigned to receive either chloroquine or Quinimax® using a computer- generated random numbers table. The treatment codes for each child were kept in sealed consecutively numbered envelopes, which were opened after parental consent had been obtained.

The two treatment schedules were:

i) Chloroquine syrup by nasogastric tube 25mg/kg total dose divided as 10mg/kg ini-

tially and 5mg/kg at 6, 24 and 48 hours from the initial dose. The chloroquine was given orally as soon as the patient regained full consciousness.

ii) Quinimax® solution 8 mg/kg of base in 10 ml/kg of 0.18 % saline in 4.3% dextrose infused over 4 hours every 8 hours on days 0, 1, and 2. This was followed by Quinimax® tablet (125mg and 250 mg), 8 mg/kg of base rounded off to the nearest half of a 125 mg scored tablet 8 hourly on days 3-6 inclusive. This was crushed, mixed with water and passed down a nasogastric tube for patients who were still unconscious. The drug was given orally as soon as the patient regained full consciousness provided at least 2 doses had already been given by intravenous infusion. The total dose of Quinimax® given was 24 mg/kg/day for 7 days.

Amodiaquine or artesunate were prescribed for cases of treatment failure. In 1999 amodiaquine, at the same dosage as chloroquine, was prescribed for patients whose treatment had failed on chloroquine, irrespective of the level of consciousness at the time. In 2000, artesunate tablets (Guilin No. 2 Pharmaceutical Factory, Guangxi, China) at a dosage of 4mg/kg stat, 1mg/kg twice daily for 2 days then 1mg/kg daily for 3 days was prescribed for those who were still unconscious at the time that a decision was taken to change treatment. The drugs were initially given by the nasogastric route till patients could swallow. Treatment failures in the patients on Quinimax® were to be treated with artesunate.

Supportive Care

All patients received supportive care as clinically indicated. Blood transfusion was given if the haemoglobin was below 5.0g/dl or if the child showed signs of clinical decompensation from acute anaemia. Hypoglycaemia was treated with IV 10% glucose 4 ml/kg. They were fed 3-hourly by nasogastric tube with local porridge containing sugar to a total fluid input of 75% of their maintenance requirement. Dehydration was corrected. Convulsions were treated with intravenous diazepam (0.3mg/kg) and prophylactic intramuscular phenobarbitone (10mg/kg stat then 2.5mg/kg 12 hourly). All patients were started on intravenous crystalline penicillin and chloramphenicol until cerebrospinal fluid could be examined to exclude meningitis.

Data Analysis

Data was analyzed using Epi Info 6.04 software. Patients were included in the analysis on an intention-to-treat basis. The patients were categorised into those receiving chloroquine and those receiving Quinimax®. For categorical data, differences were analysed with chi-square tests. For quantitative data differences were analysed by student's t-test. P values of < 0.05 were considered significant.

RESULTS

Out of 983 patients screened for recruitment into the study, 102 with peripheral parasitaemia had been in coma (BCS ≤ 3) for at least 60 minutes. 70 (33 on chloroquine, 37 on Quinimax®) fulfilled the inclusion/exclusion criteria and were followed up to at least Day 7. Fifty-eight were followed up to Day 14. The major reason for exclusion was intake of at least 20mg/kg of chloroquine prior to admission. There were 4 exclusions for abnormal cerebrospinal fluid.

Table 1 Clinical and laboratory parameters on admission according to treatment group

	Chloroquine	Quinimax®	p-value
No.	33	37	
Sex (n)	M=21, F=12	M=17, F=20	0.21
[a]Age (years)	4.0 (2.5-6.0)	5.0 (3.0-7.0)	0.64
[a]Duration of Symptoms prior to admission (Days)	3 (2-4)	3 (2-3)	0.23
*Prior chloroquine treatment (n)	12 (36.6%)	21 (56.7%)	0.14
[b]Admission temperature (°C)	38.1 (0.14)	37.9 (0.17)	0.39
[a] Blantyre Coma Score on Admission	2 (1-3)	2 (1-2)	0.16
Respiratory distress (n)	7 (21.8%)	5 (13.5%)	0.37
[b]Parasite Density (x $10^3/\mu L$)	155 (44.0)	120 (26.7)	0.49
[b]Hb (g/ dL)	7.9 (0.44)	8.1 (0.36)	0.72
Severe Anaemia (Hb $\leq$ 5.0g /dL)(n)	5 (15.1%)	4 (10.8%)	0.73
%Hypoglycaemia ($\leq$ 2.2mmol/ L)	1 (3.0%)	2 (5.4%)	1.00

[a]Median, Interquartile Range; [b]Mean, SEM. *Received <20mg/kg chloroquine prior to admission

The characteristics of the patients according to treatment assignment are shown in Table 1. The two groups were comparable with respect to various parameters at the time of admission. Even though more patients in the Quinimax® group had received chloroquine prior to admission, the difference was not statistically significant (p= 0.14).

Primary end points

Mortality (Table 2)

There were 8 deaths in the 2 groups combined, giving an overall mortality rate of 11.4%. The mortality rates for the individual groups were comparable to each other, 12.1% and 10.8% in the chloroquine group and Quinimax® group respectively (p= 1.0). Five of the eight (62.5%) deaths occurred within 48 hours of admission.

Table 2 Outcome according to treatment group

	Chloroquine	Quinimax®	p-value
No	33	37	
Fatal cases (n)	4 (12.1%)	4 (10.8%)	1.00
Neuro deficit at Day 7 (n)	4 (12.1%)	3 (8.1%)	0.70
Neuro deficit at Day 14 (n)	4 (12.1%)	2 (5.4%)	0.42
Treatment Failure (ETF and R2) (n)	5 (15.2%)	0 (0%)	**0.019**
ETF (n)	4 (12.1%)	0 (0%)	**0.045**
[a]Time to Coma Score 5 (hours)	36.0 (12.0-48.0)	36.0 (24.0-72.0)	0.13
[a]Time for fever to settle (<37.5°C)(hours)	32 (16-64)	40 (24-56)	0.93
[a]Time to parasite clearance (hours)	48.0 (48.0-72.0)	60.0(48.0-72.0))	0.91
Patients parasitaemic on Day 3 (n)	7 (21.8%)	1 (2.7%)	**0.025**

[a]Median, Interquartile range

Neurologic sequelae (Table 2)

The overall neurologic sequelae rate on day 7 was 10%, with no significant difference between the rates for each group (Chloroquine,12.1%; Quinimax®, 8.1%; p=0.70). Six of the seven patients with neurologic sequelae on day 7, were reviewed on day 14. Of these, 5 still had sequelae on day 14. The defaulting patient who had been on chloroquine and was ataxic on day 7 was assumed to be still ataxic on Day 14, thus giving an overall sequelae rate of 8.6% on day 14. The other sequelae in the chloroquine group were ataxia with slurred speech on day 7, with persistence of the latter on day 14 (1); aphasia on days 7 and 14 (1); coma on day 7 with full recovery of consciousness by day 14, but with abnormal involuntary movements of the limbs (1). The sequelae in the Quinimax® group were aphasia on day 7 with recovery of speech by day 14 (1); spasticity with aphasia on day 7 with recovery of speech and ability to sit but unable to stand by day 14 (1); visual hallucinations and ataxia on day 7 with cessation of hallucinations but persistence of ataxia by day 14 (1).

Treatment Failure (Table 2)

There were 5 treatment failures, all of which occurred in the chloroquine group (15.2%). Of the 5 treatment failures, 4 whose level of consciousness deteriorated and/or who had increasing temperature peaks on days 1, 2 or 3 in the presence of parasitaemia, were classified as ETF. One, who was asymptomatic but parasitaemic on day 7, was classified as R2 resistance. All 4 of the patients with ETF required a change in antimalarial drug on days 1, 2 or 3 (1, 2 and 1 patient(s) respectively). All the patients with treatment failures responded well to amodiaquine (3 patients) or artesunate (2 patients), with clearance of parasites in all of them, and also resolution of symptoms in the 4 patients who were symptomatic. There was a significant difference in the ETF rate between the two groups in favour of Quinimax® (p = 0.045).

There were 2 patients on chloroquine who were aparasitaemic on day 7 but were parasitaemic and asymptomatic on day 14. They qualify as possible cases of R1 resistance with early recrudescence. Due to the high default rate of 17% at day 14, it was not possible to calculate the incidence of early R1 resistance.

Secondary end points

Resolution of fever, recovery from coma, parasite clearance, parasitaemia on day 3 (Table 2)

There was no significant difference between the two groups with respect to times for fever to decline, to regain a Blantyre coma score of 5 and to clear parasites. Significantly more patients on chloroquine were parasitaemic on day 3 as compared to those on Quinimax® (p= 0.025). Only 2 of the 8 patients who were parasitaemic on day 3, both in the chloroquine group, required a change in treatment. The others were asymptomatic and cleared their parasites by day 7 without a change in treatment.

Side effects

One patient whose intravenous Quinimax® infusion ran too fast due to a faulty regulator became hypoglycaemic. None of the older children complained of symptoms suggestive of cinchonism such as tinnitus, headache, nausea or abdominal pain. This could not be excluded in the younger ones due to problems with communication. There were no major side effects attributable to chloroquine.

DISCUSSION

This study was carried out against the background of continued use of chloroquine as the drug of choice for both uncomplicated and severe malaria despite reported R2 and R3 resistance of *P. falciparum* to chloroquine in Ghana[2,4-6] and the recommendation by the WHO that parenteral quinine preparations be used to treat severe malaria in areas with chloroquine resistant parasites[10]. The continued use of chloroquine in our Department had been based on the results of local studies to monitor its effectiveness, which showed that the outcome of treatment with chloroquine was similar to that in centres using quinine, and to that of children treated with artesunate in a local comparative trial[2,11]. Since the state of drug sensitivity/resistance is dynamic rather than static, continued monitoring of the performance of chloroquine locally is important. The current study was therefore conducted to measure the performance of chloroquine against a quinine preparation, Quinimax®.

A large percentage of patients in both groups had received chloroquine (<20 mg / kg) prior to admission and though this was larger in the group on Quinimax® the difference was not statistically significant. Due to the fact that most patients seen in tertiary health facilities would have been seen earlier by other health professionals, and also due to the promotion of the initiation of antimalarial medication at home for febrile children, the high prevalence of prior chloroquine administration is not surprising.

The use of a second -line drug was necessary in 12.1% of patients on chloroquine whose clinical condition was worsening as compared to 0% in the group treated with Quinimax® (p= 0.045). In the study we conducted in 1998 comparing the efficacies of chloroquine and artesunate in the treatment of cerebral malaria (82 patients), we surprisingly had no treatment failures either with chloroquine or with artesunate[11], despite having documented an ETF rate of 11.4% for chloroquine in 1997[2] (88 patients). We stated that this was no reason for complacency about the issue of chloroquine resistant malaria in Ghana. This caution is supported by the fact that our current study shows an ETF rate of 12.1%, similar to that obtained in 1997. In a life- threatening and potentially handicapping condition such as cerebral malaria, it is unacceptable to use a drug which would be ineffective in at least 12% of cases if alternative drugs with lower treatment failure rates are available. Our current findings would therefore demand that quinine derivatives or other antimalarial drugs of equal efficacy, such as the artemisinin derivatives[16,17], be used either singly or in suitable combinations[18,19] for the treatment of cerebral malaria in Ghana rather than chloroquine. For this reason, it was decided not to attempt to achieve a larger sample size.

The overall mortality and neurological sequelae rates (11.4% and 10% respectively) for patients in this study were comparable to earlier reports from our centre[2,11] and others[10,12,13,16], which range from 15-21% for mortality and 5-15% for neurologic sequelae. The 2 treatment groups did not differ significantly for these endpoints. However, the sample size was limited for the reason stated above and thus the study had approximately only 5 % power to demonstrate a reduction from 15% to 10% mortality.

In the setting of a very low health professional to patient ratio and lack of sophisticated infusion and monitoring apparatus, the use of intravenous infusions of quinine preparations is potentially dangerous. A complication of particular concern is hypoglycaemia[10,20]. English *et al* found that 9% of their patients treated with quinine and concurrent 4% dextrose infusion became hypoglycaemic[21]. We were able to avoid episodes of hypoglycaemia, except in one patient whose infusion ran too fast, by infusing Quinimax® in a 4.3% dextrose solution and by 3–hourly nasogastric feeding of patients who were not vomiting or did not have ileus, with a local corn porridge with added sugar. Nasogastric feeding has been standard practice in the management of cerebral malaria in our Department for at least a decade[2,11,22] and aspiration of feeds has not been observed. We would advocate the administration of quinine preparations by the intramuscular route[10] rather than the intravenous, and nasogastric feeding of porridge with sugar for the prevention of hypoglycaemia to Ghanaian children with cerebral malaria because these routes are simpler and safer under the conditions of severe shortage of staff and facilities that we work. However, due precautions should be taken to prevent injection associated infections[23] by adherence to aseptic technique, and patients at higher risk of vomiting as indicated above, should be excluded from nasogastric feeding. The successful development of suitable rectal formulations of quinine salts would greatly facilitate the safe administration of these drugs. Barennes *et al* have shown that Quinimax® injection solution is equally efficacious when given intrarectally as when given by infusion[12]. The overall tolerance and efficacy of quinine solution given intrarectally has also been shown to be good[24].

CONCLUSION

Treatment failures are more likely in Ghanaian children with cerebral malaria who are treated with chloroquine than in those treated with Quinimax®. We therefore recommend that quinine salts or other antimalarial drugs of equal efficacy be used to treat cerebral malaria in Ghana. Research into suitable formulations and dosage regimens for rectal administration of quinine salts and other antimalarial drugs is indicated for use in countries with poorly resourced health services. This will facilitate safe and early administration of effective drugs to children suffering from severe malaria.

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