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Comparative trial of oral versus intramuscular chloroquine in children with cerebral malaria

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Abstract

One hundred and thirteen children aged 12 years or less with cerebral malaria in Accra, Ghana were treated with chloroquine either with a low dose regime of 3·5 mg/kg 8-hourly intramuscularly, or orally by nasogastric tube, in a standard regime, both to a total of 25 mg/kg body weight. There was no obvious difference in outcome in the 2 treatment groups. The overall mortality of 5·3% (5·9% and 4·4% in the oral and intramuscular treatment groups respectively) was similar to that seen 10 years ago in this hospital. The average parasite clearance time had increased to 61 h, compared to 41 h noted 10 years ago. The incidence of hypoglycaemia (3%) was very low compared to studies in other malaria endemic areas. The reason for this is not clear but it could have contributed to the low mortality. Neurological deficits were seen on day 14 in 7·8% of patients. Parasitaemia recurred within 14 d in 22% of surviving patients, confirming the presence of RI/RII chloroquine resistance in Accra.

Introduction

Chloroquine has been the drug of choice in Ghana for uncomplicated and complicated malaria for many years. Recently, *Plasmodium falciparum* malaria with reduced sensitivity to chloroquine (RI and RII resistance) has been reported in Ghana (NEEQUAYE, 1986; NEEQUAYE *et al.*, 1988; OFORI-ADJEI *et al.*, 1988). In 1989 it was decided to study cases of cerebral malaria in children with regard to clinical features and outcome in the light of this reduced sensitivity. At the time clinical practice in our hospital was to treat such patients with either chloroquine 5 mg/kg body weight intramuscularly (im) 12-hourly to a total of 25 mg/kg or orally by nasogastric tube in the standard regime of 10 mg/kg followed 6, 24 and 48 h later by doses of 5 mg/kg each. As there has been controversy over the use of im chloroquine (OFORI-ADJEI *et al.*, 1984; TRIGG *et al.*, 1984), especially with regard to its side effect of hypotension, we decided to use the low dose im regime of 3·5 mg/kg 8-hourly to a total dose of 24·5 mg/kg recommended in the Ghana National Formulary (COEN *et al.*, 1988) and to compare the 2 routes of administration in relation to outcome of disease. The national recommendation and our study preceded the publication of the World Health Organization recommended dose of 3·5 mg 6-hourly (WHO, 1990). In our busy wards, as in many other African countries, the large number of patients and the shortage of nursing staff demands the search for alternative routes of administration of chloroquine. We considered nasogastric and im administration to be operationally more efficient than intravenous administration.

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Methods

Study site and patients

This prospective study took place in the children's block of the Korle Bu Teaching Hospital, Accra, Ghana between March and August 1989. Ethical clearance was given by the research committee of the University of Ghana Medical School. All children of 12 years or under who were admitted under 2 of the 3 paediatric teams with a diagnosis of cerebral malaria, 113 in all, were entered in the study. Diagnosis was based on the presence of unrousable coma associated with asexual *P. falciparum* parasitaemia, excluding other encephalopathies such as hypoglycaemia, meningoencephalitis or head injury. If a generalized convulsion had occurred then coma must have persisted for more than 6 h afterwards, to exclude post-ictal sleep (WHO, 1986). All patients admitted during one week (0800 h Monday–0800 h Monday) received intramuscular chloroquine and all patients admitted during the following week had nasogastric chloroquine. This alternate week regime was continued throughout the study.

Clinical management

A complete medical history was taken and a full clinical and neurological examination was made on admission, noting the degree of coma using the Glasgow coma scale (TEASDALE & JENNETT, 1974). All patients were weighed and their temperature recorded. A lumbar puncture was performed in all patients to exclude meningoencephalitis. A cell count and culture were carried out on the cerebrospinal fluid, which was also analysed for protein. Blood samples were taken for malaria parasite count and species identification. Baseline samples for blood urea and electrolytes, blood glucose, serum bilirubin, haemoglobin, haemoglobin electrophoresis, and glucose-6-phosphate dehydrogenase (G6PD) were taken from as many patients as possible. Initial blood glucose was also estimated by Dextrostix® (Ames, London, UK). Thick and thin blood films were stained with Giemsa's stain. Parasite counts were estimated by counting the number of trophozoites per 400 white cells on the thick film and converting this to parasites/μl of blood, assuming a mean white cell count of 6000/μl. Because of the difficulty of accurately counting parasites in thick films with heavy parasitaemia, the parasite count were converted to the Bruce-Chwatt parasite density index (PDI) (WHO, 1984).

Patients in both treatment groups were nursed in the general wards with the same medical and nursing staff and management was kept as simple as possible. Apart from the different routes of chloroquine administration all other treatment was similar in both groups. Patients were nursed on their sides while unconscious. They were fed 3–4 hourly by nasogastric tube with local porridge containing sugar to a total fluid input of 75% of their expected requirement, taking into account the state of hydration., If severe dehydration was present this was corrected intravenously simultaneously. Blood transfusion was given if there was severe anaemia of 6·5 g/dl or below. Hypoglycaemia on admission was treated with a bolus of intravenous 50% dextrose (1 ml per kilogram body weight). This was also given if blood sugar results were not immediately available.

Convulsions were treated with intravenous diazepam and prophylactic phenobarbitone 5 mg/kg per 24 h if necessary. Pyrexia was controlled by sponging with cool water and fanning.

Drug treatment

Chloroquine phosphate therapy was started immediately after the initial smear for malaria parasites had been taken. It was given either im in a dose of 3·5 mg/kg 8-hourly for 7 doses or as a syrup (80 mg base/5 ml) via nasogastric tube in an initial dose of 10 mg base/kg, followed by 5 mg base/kg at 6, 24 and 48 h. If a child in the second group regained full consciousness, chloroquine was continued orally. All patients were admitted at least until they had completed the chloroquine course. They were then asked to come for follow-up daily until day 7 and then at weekly intervals up to day 60.

Statistics and calculations

A statistical package (Epi-Info, version 5) (DEAN *et al.*, 1990) was used to analyse the data. Parasite clearance time was calculated as the time until the first negative blood smear. The time for the temperature to remain normal for 12 h was calculated (WHITE & KRISHNA, 1989), as also was the time to full consciousness.

Results

The numbers and sexes of the children in the 2 treatment groups are shown in Table 1. Vomiting was not observed in any of the children. However, aspiration pneumonia was suspected in one child receiving im chloroquine who died. There was no significant difference between the oral and im groups in any of the data shown in Tables 1 and 2. Six patients died (5%), 4 (6%) in the oral group and 2 (4%) in the im group. They are compared with the survivors in Table 3. The mortality rate in the 2 treatment groups was not significantly different (Fisher's exact test, $P<0·55$ for single tail). Fifty-four percent of the oral group and 47% of the im group had received some form of drug treatment before presenting at our hospital.

The initial trophozoite count was not done in 12 patients (11%), but these patients were entered in the study on the basis of clinical suspicion and subsequent demonstrations of parasitaemia. The degree of parasitaemia did not differ in the 2 treatment groups. Of the 37 children receiving 40 ml/kg of whole blood, 26 did so in the first 24 h. Blood glucose and/or Dextrostix® estimation was done on admission in 75 patients, and the incidence of hypoglycaemia (below 2·2 mmol/litre) was 3% (2 patients). The patients whose blood sugar was not estimated did not differ clinically from those who were tested. One of the hypoglycaemic patients died. Cerebrospinal fluid was normal in all except one patient, who had a raised protein level.

Table 1. Clinical and laboratory findings in the two treatment groups

	Group	
	Oral	Intramuscular
Number of subjects	68	45
Sex (male:female)	44:24	23:22
Age (months)	60·4±30·6	61·6±28·9
Duration of illness before admission (d)	2·5± 1·4	2·8± 1·6
Self-medication	37 (54·4%)	21 (46·7%)
Convulsion	51 (75%)	34 (75·6%)
'Coca-cola' urine	9 (13·2%)	4 (8·9%)
Temperature		
<37·5	9	8
37·5–39	54	29
>39	5	8
Glasgow coma scale		
Eye opening	2·9±1·2	2·9±0·9
Best verbal response	3·9±1·2	3·9±1·0
Best motor response	2·9±1·1	3·0±1·0
Jaundice	24 (35·3%)	19 (42·2%)
Dehydration	6 (8·8%)	6 (13·3%)
Hepatomegaly	43 (63·2%)	21 (46·7%)
Splenomegaly	30 (44·1%)	12 (26·7%)
Haemoglobin on admission (g/dl)	7·7±2·0	7·8±2·0
Haemoglobin <6·5 g/dl	16 (23·5%)	10 (22·2%)
Glucose (mmol/litre)	6·0±2·1[a]	6·1±2·8[b]
Dextrose (mmol/litre)	6·9±2·4[c]	7·1±2·5[d]
Initial parasite count (Bruce-Chwatt's PDI)	7·6±2·7	7·4±2·8

[a] $n=30$
[b] $n=16$
[c] $n=32$
[d] $n=24$

Table 2. Indications of outcome in the two treatment groups

	Group	
	Oral	Intramuscular
Mean parasite clearance time (h)	58·3±33·3	62·1±35·2
Median time to regain full conciousness (h)	33·0	36·0
Temperature clearance time (h)		
Mean	71·4±38·4	65·8±52·4
Median	66	48
Recurrence of parasitaemia by day 14	15/51 (29·4%)	9/35 (25·7%)
Neurological deficit		
Day 7	11/58 (16·2%)	5/42 (11·1%)
Day 14	5/50 (10·0%)	4/33 (12·1%)
Blood transfusion	19/68 (27·9%)	16/45 (35·6%)
Duration of admission (d)	6·3±4·5	6·9±3·8
Outcome of illness		
Died	4 (5·9%)	2 (4·4%)
Survived	64 (94·1%)	43 (95·6%)

Table 3. Clinical and laboratory findings in survivors and non-survivors

	Group	
	Died	Survived
Number of subjects	6	107
Sex (male:female)	5:1	62:45
Age (months)	62±9	60·8±30·6
Duration of illness before admission (d)	2·4±1·1	2·7± 1·5
Self-medication with chloroquine	3 (50%)	55 (51·4%)
'Coca-cola' urine	–	13 (12·1)*
Temperature		
<37·5	–	17 (15·9%)
37·5–39	6 100%)	77 (72·0%)
>39	–	13 (12·1%)
Jaundice	1 (16·7%)	42 (39·3%)
Hepatomegaly	4 (66·6%)	60 (56·1%)c
Splenomegaly	3 (50%)	39 (36·5%)
Initial parasite count (Bruce-Chwatt's PDI)	6·5±2·9	7·5±2·7
Haemoglobin on admission (g/dl)	7·1±1·4	7·8±2·0
Haemoglobin <6·5 mg/dl	2 (33·3%)	24 (22·4%)
Glucose on admission	4·7±3·4	6·1±2·3
Dextrose on admission	8·1±1·3	6·9±2·5
Glasgow coma scale		
Eye opening	2·8±2·0	2·9±1·0
Best verbal response	4·7±0·8	3·9±1·0
Best motor response	3·1±3·0	3·0±0·9
Route of administration of chloroquine		
Oral	4 (66·7%)	64 (59·8%)
Intramuscular	2 (33·3%)	43 (40·2%)
Duration of admission (d)	1·5±0·7	6·8±4·2

The full Glasgow coma scale (GCS) was applied on admission to 110 patients. The differences between the 2 treatment groups are shown in Table 1. The results for eye opening were considered unreliable as the junior doctors found it difficult to differentiate between spontaneous eye opening and the many unconscious patients with their eyes open. Forty per cent gave no 'best verbal response', 26% were incomprehensible, 24% made an inappropriate response and 10% were confused. Six per cent had no 'best motor response', 28% extended, 29% flexed, and 26% could localize pain. No patient could obey commands. The best motor response was clinically the easiest to evaluate, but neither the total score nor the individual components correlated with outcome or time to full consciousness. Of the 6 patients who died, 2 could localize pain on admission, 2 were flexing, one was extending, and in one there was no response. The mortality rate of those who could not localize pain was 6·5%, but this did not differ significantly from the whole group.

There was no significant difference between the oral and im groups in their mean parasite clearance time, the mean time to the temperature settling for 12 h and the median time to regaining full consciousness (Table 2). Overall, 70% had regained consciousness by 48 h. Neurological examination on day 7 of 100 children revealed a deficit in 16 (16%) of them, 11/58 (16%) in the oral group and 5/42 (11%) in the im group. Neurological deficit was still present on day 14 in 9/83 cases (11%). Seven of these children still had a severe deficit when last seen on days 16 (2 children), 20, 28, 35, 42 and 60 respectively. Six had increased tone and were stiff with brisk reflexes, 5 could not walk, 4 could not sit, 3 could not speak, 2 were blind, 2 were deaf, one had recurrent convulsions, and one was hyperactive.

Parasitaemia with trophozoites recurred in 24 (28%) of the 86 patients who attended for follow-up, 15/51 (29%) in the oral group and 9/35 (26%) in the im group. Recurrence occurred between days 3 and 7 in 3 patients (2 in the oral group and 1 in the im group), between days 8 and 14 in 17 (10 oral, 7 im) and between days 15 and 23 in 4 (2 in each group). Fifteen patients had fever, 2 had headache and 7 were well at the time of recurrence. Patients were treated, with amodiaquine (15), a second course of chloroquine (7) or sulfadoxine-pyrimethamine (2), usually as outpatients. Of the 7 patients re-treated with chloroquine, 2 cleared their parasitaemia, 3 absconded and 2 relapsed again and were treated with amodiaquine. One of these relapsed a third time and was given sulfadoxine/pyrimethamine. Of the 15 treated with amodiaquine, parasitaemia cleared in 11. Of the 4 who relapsed a second time, 2 were cleared with a second course of amodiaquine, one with chloroquine and one with sulfadoxine/pyrimethamine. The other patient given sulfadoxine/pyrimethamine relapsed a third time and received oral quinine in hospital.

Table 3 compares the clinical and laboratory findings in patients who survived and those who died. There was no difference in the Glasgow coma scale scores in the 2 groups. One of the children who died in the im group was suspected to have suffered from aspiration pneumonia. Hypoglycaemia was noted in one of the children who died in the oral group.

Discussion

Our results suggest that there is no difference in outcome between chloroquine administered orally by nasogastric tube or im in children suffering from cerebral malaria. It has been shown by WHITE *et al* (1988) that chloroquine given by nasogastric tube was absorbed well even in comatose children; there were no deaths in the small group of 4 children with cerebral malaria treated in this manner.

Six of the 113 children in our study died (5%). This was comparable to the mortality rate of 5% found in a study done in the same department in 1979, using a treatment regime of im chloroquine (5 mg/kg) followed by oral chloroquine when the patient regained consciousness and also using intravenous mannitol and dexamethasone (COMMEY *et al.*, 1980). At that time there was no evidence of reduced sensitivity to chloroquine in Ghana. In our study the average parasite clearance time was longer (61 h) than the 41 h reported in 1979. Since then OFORI-ADJEI *et al.* (1980) have reported a prolonged parasite clearance time. In 1989, 68% of patients had regained full consciousness by 48 h, compared to 74% in 1979 (no significant difference).

The mortality rate in both these studies was much lower than that reported in some other countries. In Thailand the mortality rate of 28 children with cerebral malaria was 21% (WARRELL *et al.*, 1982) and in Malawi it was 16% (TAYLOR *et al.*, 1988). In both these studies intravenous quinine was used. In The Gambia, 22% of 19 patients with cerebral malaria and treated with chloroquine died (WHITE *et al.*, 1987).

High mortality in cerebral and severe malaria is associated with hypoglycaemia (blood sugar <2·2 mmol/litre) (TAYLOR *et al.*, 1988; WHITE *et al.*, 1987). The incidence of hypoglycaemia in our series was very low (3%), compared to 23% in Malawian children (MOLYNEUX *et al.*, 1989) and 32% in Gambian children with severe malaria (WHITE *et al.*, 1987).

The mean duration of illness before admission was similar to that in Malawi reported by TAYLOR *et al.* (1988).Many of our patients (51%) had been given some medication before arrival at hospital, which could have included an antimalarial. Self medication with chloroquine is common (OFORI-ADJEI *et al.*, 1984). It is possible that early treatment at home or at a primary health care facility contributed to the low incidence of hypoglycaemia.

Our low mortality rate does not seem to be due to different selection of patients. All had unrousable coma and, if they had had a convulsion, were unconscious for at least 6 h afterwards; 33% had repeated convulsions. All our patients had Glasgow coma scores correlating with those reported by WARRELL *et al.* (1982), in that the best motor response was localizing or worse. We agree with NEWTON *et al.* (1990) that this component of the score is the easiest to estimate. Our study was commenced before MOLYNEUX *et al.* (1989) described a modified coma scale for young children. We found that the full Glasgow coma scale was easy for experienced paediatricians to apply to children, but less experienced doctors had difficulty with the eye opening response. More precise instructions are given by MOLYNEUX *et al.* (1989).

Anaemia was an important feature of our patients' illness; 26 (23%) were severely anaemic (haemoglobin <6·5 g/litre), including 2 of the 6 who died. Thirty-seven patients (33%) were transfused, and without transfusion many might have died. MOLYNEUX *et al.* (1989) found that patients needing transfusion took significantly longer to gain full consciousness. In our patients, the mean time taken to regain full consciousness was similar in those patients transfused in the first 24 h and those not transfused.

The neurological deficit rate of 7·8% of our patients on day 14 was similar to that of 6·8% of normoglycaemic Malawian children but less than the 37% of hypoglycaemic children (TAYLOR *et al.*, 1988). Those who did not attend for follow-up on day 14 were assumed to have recovered. Sequelae on day 7 have increased significantly since 1979 ($P<0·02$), possibly as a result of slower parasite clearance.

Parasitaemia recurred in 29% and 26%, respectively, of the children in the oral and im groups seen on day 14, confirming the presence of RI and RII resistance to chloroquine in Accra. This finding was consistent with that reported by AFARI *et al.* (1989). No case of RIII resistance to chloroquine was seen. We cannot comment on resistance to the second line drugs used to treat relapse in this study, since the patients were not admitted to hospital, but we have previously documented a case of resistance *in vivo* to amodiaquine at the RI level (NEEQUAYE *et al.*, 1988) and AKANMORI *et al.* (1989) have recently found resistance *in vitro* to amodiaquine and sulfadoxine/pyrimethamine in Accra.

The low overall mortality rate in our study could have masked any difference in efficacy. Despite the emergence of resistant strains of *P. falciparum* in the study area, therapeutic response to chloroquine was good in both groups. Neither route of administration was associated with complications such as aspiration pneumonia or injection abcess. So far, chloroquine remains the drug of choice for severe malaria in Ghana, and either of the 2 simple treatment schedules described may be used, with results that compare favourably with other studies described. Operationally, oral administration should be preferred as it is easier to administer via nasogastric tube to unconscious patients, cheaper, and spares the children from injections. The good primary health care facilities in Accra may have contributed to the low mortality. However, the situation has to be monitored in case RIII resistance to chloroquine emerges. Information needs to be continually revised in order to guide clinicians as to the best management of cerebral malaria in a changing situation.

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Announcement

The second 'residential meeting' of the Royal Society of Tropical Medicine and Hygiene (to include the Annual General Meeting) and other European Societies of Tropical Medicine will be held at the Royal College of Physicians of Edinburgh, Scotland from Monday 5th to Wednesday 7th July 1993. Accommodation will be on the University campus or alternatively in hotels near the City centre. Full social programme including reception and banquet. Further details available shortly from the Administrator, Royal Society of Tropical Medicine and Hygiene, Manson House, 26 Portland Place, London, W1N 4EY (Tel: 071 580 2127; Fax: 071 436 1389).