ORAL CHLOROQUINE IN THE TREATMENT OF CEREBRAL MALARIA IN GHANAIAN CHILDREN

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SUMMARY

The usefulness of chloroquine as the first line drug for the treatment of acute simple and complicated malaria has been threatened in many Sub-Saharan African countries by the emergency of *P. falciparum* resistant to chloroquine. In Ghana, anecdotal and published reports suggested that resistance was becoming a major clinical problem[1,2,3], although it remained the first line treatment for simple and complicated malaria including cerebral malaria. This study was undertaken in 1997 to determine the effectiveness of chloroquine in cerebral malaria. Between July and August 1997, 196 children with cerebral malaria were admitted to the Children's Emergency Ward of the Korle Bu Teaching Hospital, Accra. Mortality was 15.3%. Eighty-eight treated initially with chloroquine were studied to Day 7 or longer. Thirty-one of 60 (52%) children tested had parasites in their peripheral blood film at Day 3. In 3 (5%) the parasitaemia was >25% of the Day zero value (RII resistance) but 2 of these were well. Taking clinical parameters such as fever and worsening coma score into consideration early treatment failure occurred in 10 patients (11.4%) and these had their treatment changed to amodiaquine. The results indicate that resistance to chloroquine is demonstrably increasing.

Keywords: Chloroquine, cerebral malaria, quinine

INTRODUCTION

The usefulness of chloroquine as the antimalarial drug of choice in Sub-Saharan Africa has been threatened by the emergency of resistant strains of *P. falciparum*. A 1989 study in Ghana showed that chloroquine either orally, by nasogastric tube, or intramuscularly (25mg/kg total dose) was effective in treating cerebral malaria in children[1]. Resistance at the RI/RII level was seen in 22% but there was no RIII resistance. Since then in vivo and in vitro studies in Ghana have shown the presence of RII and RIII resistance[2,3,4]. However chloroquine has remained the recommended first line treatment for malaria including cerebral malaria in Ghana. This study was done because clinicians were worried that the National Policy of using chloroquine for severe malaria was outdated in the light of increasing chloroquine resistance and the World Health Organization's recommendation that i.v. quinine and now i.m. artesunate should be used for cerebral malaria. The study was therefore carried out with a view to possibly changing the guidelines for treatment of cerebral malaria in southern Ghana.

METHOD

Children attending the children's Emergency Ward of the Korle Bu Teaching Hospital diagnosed as cerebral malaria between July and August 1997 were studied. The study was approved by the Ethical Review Committee of the University of Ghana Medical School. The consent of parents and guardians was obtained before the children were included in the study. The diagnosis of cerebral malaria was based on the presence of unrousable coma (Blantyre Coma Scale of 3 or less as published by Molyneux et al[5]) associated with asexual *P. falciparum* parasitaemia, excluding other encephalopathies such as hypoglycaemia, meningoecephalitis or head injury. Children with post convulsive coma were included if unconsciousness had persisted for more than 30 minutes after the convulsion.

Patients satisfying the inclusion criteria were admitted and their clinical, parasitological and neurological conditions monitored daily. All patients had a full clinical history and examination, together with estimation of blood sugar, and lumbar puncture for examination of cerebro-spinal fluid. Giemsa stained thick and thin blood smears for parasite identifica-

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tion and counting were done on admission. Parasites were counted per 200 white blood cells (W.B.C.) divided by 200 and multiplied by the W.B.C. count to convert it to the count per microlitre. Thereafter parasite counts were done daily until parasites cleared, and on Day 7. The Blantyre coma scale was used to assess neurological status on admission and until the children regained full consciousness.

All patients received chloroquine orally via a nasogastric tube at an initial dose of 10mg/kg base, followed by 5mg/kg at 6, 24 and 48 hours. Patients were fed through the nasogastric tube with sweetened local porridge to prevent hypoglycaemia and were nursed on their sides. Hypoglycaemia was treated with a bolus of 4ml/kg of iv 10% dextrose. Fluid input was 75% of their expected requirement unless they were clinically dehydrated, when intravenous supplements were used for correction. Convulsions were treated with i.v. diazepam (0.3mg/kg) and prophylactic phenobarbitone (10mg/kg stat then 2.5mg/kg 12 hourly) if necessary. Fever was controlled with paracetamol, and sponging with cool water.

If a patient's condition was thought on clinical grounds to be worsening, treatment with chloroquine was changed to oral amodiaquine or parenteral quinine. Clinical parameters used in assessing a worsening state were fever and state of consciousness. Parasite counts were also used to guide the clinician in his judgement. Patients were included for evaluation of efficacy if follow-up was completed to Day 7. The Day 7 end-point was chosen because the study was interested in early treatment failure. Results are presented as proportions (%), or mean (standard deviation).

RESULTS

During the period of the study, July through August 1997, 906 children with malaria were admitted to the Children Emergency Ward. One hundred and ninety-six were diagnosed as cerebral malaria. Thirty of these died (15.3%). Eighty-eight of these children aged between one and 12 years were studied to Day 7 although 28 went home when they regained consciousness due to shortage of beds. In these, Day 3 parasite counts were not done although they returned on Day 7. The others (78 patients) went home well but were lost to follow-up.

Of the patients studied 49(56%) were males and 39 (44%) were females. Mean Blantyre coma score on admission was 2.3 (S.D.1.4 mode 2.0). Mean haemoglobin levels on admission were 8.5 (S.D..2.3) and 7.6 (S.D.1.8)g/dl for boys and girls respectively. *P. falciparum* was the sole malaria species identified in all the children. Mean parasite count was 71.6 x 10^3/microlitre (11.2 x 10^3). Day 3 parasitaemia was determined in 60 (68%) of the children. Thirty-one of the 60 (52%) had parasites in their peripheral blood film. In 3 of these (5%) the parasite count was greater than 25% of the Day zero value. By definition this was RIII resistance. One of these was treated with amodiaquine on Day 4 because of persisting fever, the other 2 were well but still had parasitaemia on Day 7 and were given amodiaquine.

Nine other patients were treated with amodiaquine, 2 on Day 2, 5 on Day 3, one on Day 4 and one on Day 7. The two treated on Day 2 had high fever and worsening coma score. Those treated on Day 3 all had persisting high fever, and 3 had worsening coma score and still had malarial parasites, although the parasite count was less than 25% of Day zero values in these cases. The patient changed to amodiaquine on Day 4 had fever and persisting parasitaemia. The first seven patients were regarded as early treatment failures on clinical grounds. The total number of early treatment failures was 10 (11.4%) that is, those with RII resistance plus those whose clinical condition worsened by Day 3.[6]

DISCUSSION

This study demonstrated a dynamic situation, in that whereas previously in 1989 in Accra, we had shown chloroquine resistance at the RI and RII level in children with cerebral malaria, in 1997 we found 5% of patients with RIII resistance (more than 25% of Day zero parasitaemia on Day 3). This is the first time this has been reported in patients with Cerebral Malaria in Ghana. In total, 11.4% of the study population had early treatment failure. However 2 of the 3 with RIII resistance were clinically better. We found that clinical parameters such as fever, and coma score were equally important as parasite counts when monitoring the patients' condition. This could by due to sequestration of parasites so that the degree of parasitaemia does not always reflect the severity of disease.

Mortality in this study had increased. It was 5.3% in 1989[1] and 15% in this 1997 study. However it was still comparable with mortality in other African countries using i.v. quinine, and more recently artesunate. Figures from Malawi show a mortality of 16%,[7] from the Gambia 22%[8] and 21.5%[9] using i.v. quinine and 20.5% with artesunate[9]. In Nigeria,[10] 17% of children with cerebral malaria treated with quinimax (96% quinine) died. This figure was cal-

culated after shocked or very anaemic children were excluded. Our study included all such patients and therefore mortality could be expected to be higher.

At the moment even though RIII resistance is present, mortality is comparable to that in other countries using i.v. quinine or artesunate. Chloroquine continues to be an effective and easy to use antimalarial for cerebral malaria in southern Ghana. Intravenous quinine as recommended treatment for cerebral malaria is very difficult to use correctly, as it has to be given as an infusion over a defined period of time and therefore closely supervised, and the patients monitored for complications such as hypoglycaemia. When there are no intensive care facilities and shortage of nursing staff and equipment, it is all too easy for mistakes to be made especially when large numbers of patients who are critically ill are admitted over a short period of time. In rural areas and small hospitals the situation is even worse and what is needed is treatment which can be administered under these circumstances. This why, currently we continue to use chloroquine for cerebral malaria, although the situation is under constant review.

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