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INTRAVASCULAR HAEMOLYSIS FOLLOWING TREATMENT OF MALARIA WITH HALOFANTRINE: CASE REPORT

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INTRODUCTION

Halofantrine is a phenanthrene-methanol antimalarial drug with proven efficacy in the treatment of multidrug resistant falciparum malaria[1]. The drug is well tolerated in Nigerian children[2]. As part of larger controlled clinical trials we treated 92 children with halofantrine but two of these children adversely reacted with intravascular haemolysis. Urinalysis, blood biochemistry and haematological parameters were normal in both children at entry.

Case 1:

The 12 years old boy had been enrolled into a larger study comparing efficacy of chloroquine-chlorpheniramine *vs* halofantrine. He presented with 2 day history of fever and anorexia. No history of prior drug ingestion and no history of adverse drug reaction or any significant family history. The major finding on examination was elevated temperature of 38.9°C. Liver and spleen were not palpably enlarged.

Blood film revealed 44.281 asexual form of *Plasmodium falciparum* per microlitre of blood. The haematocrit was 34% and, total white cell count of 4,600 per cubic mm and absolute neutrophil count of 2,522 per cubic mm were obtained. His haemoglobin genotype was AA and glucose-6 phosphate dehydrogenase activity was normal. He received halofantrine at a dose of 8 mg/kg at 6 hours interval to complete a total dose of 24 mg/kg in 12 hours.

On day 2 of follow-up, he complained of having passed dark urine twice the previous night. History of reduced urinary output was not obtained and systemic review was not contributory. On examination he appeared more ill, pale but anicteric and not dehydrated. Temperature had increased to 37.8°C compared to Day 1 temperature of 36.7°C. Blood film revealed 78 asexual forms of *P. falciparum* per microlitre of blood, a significant reduction from day 0 count of 44,281. He produced dark urine during the course of observation and this tested positive for blood on urinalysis. The haematocrit of same day was 24%.

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He was kept under observation while encouraging liberal fluid intake. He was allowed home after 8 hours following improvement of symptom.

Case 2:

A 5.5 years old Nigerian boy weighing 14 kg was enrolled into the clinical trial of halofantrine *vs.* chloroquine *vs.* pyrimethamine-sulphadoxine in the treatment of falciparum malaria in children. He had presented with 3 days history of headache, fever, chills, anorexia and vomiting. Attacks of malaria in the past were usually treated with chloroquine without deleterious effects. He was not on any malaria chemoprophylaxis and had not taken any antimalarial drug in the two weeks preceding presentation. The temperature at presentation was 37.7°C. He was neither pale nor icteric. Blood film confirmed *Plasmodium falciparum* parasitaemia with a parasite density of 78,286 asexual forms per microlitre of blood. He was treated with 3 doses of halofantrine at a dose of 8 mg per kg body weight at 6 hours interval. At about 16 hours after commencement of therapy, the child was noticed to be passing dark coloured urine. He looked more ill than at presentation and temperature was found to be 39.2°C. The haematocrit had dropped from 35% on day 0 to 20% and urinalysis was positive for blood. The haemoglobin genotype was AA and the Glucose-6 Phosphate Dehydrogenase status was normal (reconfirmed 3 months after the illness). He was observed in the clinic and later on outpatient basis following improved condition with fluid therapy.

DISCUSSION

Halofantrine has structural similarity to quinine, both been aryl-methanol. It has been suggested that haemolytic response to quinine may involve immune-lysis of quinine sensitized erythrocytes. Drugs like quinine may also cause severe haemolysis in patients with G6PD deficiency these patients were not G6PD deficient. We think that the haemolysis was an immune-lysis, antedated by previous ingestion of quinine and/or halofantrine. In Nigeria, any drug could be obtained over the counter, and even some food drinks contain sub-therapeutic dose of quinine.

Halofantrine produces deleterious cardiac effects[4, 5] but had remained well tolerated in children[2]. Anaemia is often seen in children with acute uncomplicated malaria. Hence the need to take precaution against further blood loss in this group of patients. The use of halofantrine in the treatment of malaria in West Africa is likely to increase with the advent of strains of *Plasmodium falciparum* resistant to chloroquine and pyrimethamine-sulphadoxine. This report underscores the need for clinicians to watch out for this potentially serious adverse effect of halofantrine. The cases reported by Vachom *et al* and Mofon *et al*[3,6] required haemodialysis to treat acute renal failure thus further impressing the need for vigilance.

These two cases were the first reported cases of halofantrine induced intravascular haemolysis in Nigeria and so far all those reported elsewhere occurred in adults.

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