Brief Report

Oral Artesunate–Amodiaquine and Artemether–Lumefantrine in the Treatment of Uncomplicated Hyperparasitaemic *Plasmodium falciparum* Malaria in Children

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Summary

The therapeutic efficacy, changes in haematocrit and declines in parasitaemias were evaluated in 56 children with uncomplicated falciparum hyperparasitaemia after oral artesunate–amodiaquine or artemether–lumefantrine. All children recovered clinically within 2 days and without progression to severe malaria. Falls in haematocrit in the first 3 days after treatment began were similar and <5%. Declines in parasitaemias were monoexponential with both treatments with an estimated half-life of 1 h.

Key words: artemisinin-based combinations, hyperparasitaemia, efficacy.

Introduction

Plasmodium falciparum hyperparasitaemia (*Pf*HP, >250 000 asexual parasites/μl blood or >4% parasitized erythrocytes) [1], a feature of severe childhood malaria, may require intravenous antimalarials. *Pf*HP may not be accompanied by other features of severe malaria, and oral artesunate is considered more effective than intravenous quinine in *Pf*HP in low transmission setting [2]. The present study compared the treatment efficacies, changes in haematocrit and kinetics of hyperparasitaemia in children given oral artesunate–amodiaquine or artemether–lumefantrine.

Patients and Methods

The study was done in Ibadan, Nigeria, from April 2009 to January 2011. Criteria for selection were as follows: age ≤12 years; symptoms compatible of acute uncomplicated malaria e.g. anorexia, vomiting or abdominal discomfort; *P. falciparum* parasitaemia >250 000 μl^{-1}; body temperature >37.4°C or history of fever in the 24–48 h preceding presentation; absence of other concomitant illness; no history of antimalarial drug use in the 2 weeks preceding presentation; and written informed consent given by parents or guardians. Patients with severe malaria [1] (apart from hyperparasitaemia), severe malnutrition, serious underlying diseases and known allergy to study drugs were excluded. Ethical approval was granted by the local ethics committee. History of illness was taken and a full physical examination was done by a physician.

Patients were randomly assigned to artemether–lumefantrine or artesunate–amodiaquine given according to body weight [3]. Paracetamol tablets, 10–15 mg kg^{-1} were given every 8 h for 24 h. Follow-up (clinical and parasitological) was done at 0, 1, 2, 4, 8, 16, 24 h after treatment, and on days 2–7, 14, 21, 28, 35 and 42 in 26 children and in the remainder on days 1–7, 14, 21, 28, 35 and 42. Response to treatment, parasite and fever clearance times were as previously described [3]. Cure rates were the percentages of patients whose asexual parasitaemia cleared from peripheral blood and who were free of parasitaemia on days 14–42.

Blood films (from a finger prick) were Giemsa stained and examined by light microscopy. Haematocrit was estimated before and after treatment. Blood electrolytes, urea and creatinine were measured at enrolment. Fall in hematocrit (FIH) per one thousand parasites cleared from peripheral blood (FIH/1000 parasites cpb) was calculated as the difference in haematocrit values before treatment and the first 1–2 days after treatment began as numerator, and the corresponding difference in parasitaemia as the denominator and expressing it per 1000 parasites cleared from peripheral blood. Haematocrit

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conservation was the ratio of FIH/1000 parasites cpb at a particular level of parasitemia and below divided by the corresponding value of FIH/1000 cpb for parasitemias above this level. The kinetics of parasitaemia was estimated using a non-compartmental model [4]. Data were analyzed using the statistical programme *SPSS for Windows* version 10.01 [5].

Results

In all, 24 of 56 children recruited were febrile, none had icterus or vital organ dysfunction. The enrolment characteristics of the two treatment groups were similar (Table 1). All children recovered clinically within 2 days and without progression to severe malaria (Table 2). Rate of reappearance of parasitaemia in artesunate–amodiaquine (1 child) and artemether–lumefantrine (6 children) between days 28 and 42 were similar (Kaplan–Meier survival analysis: $p = 0.11$). Twelve children, 7 in artesunate–amodiaquine and 5 in artemether–lumefantrie groups, reported adverse events; the most frequent (>4%) was vomiting.

FIH was $4.6 \pm 2.2\%$ (range 1–9) and was similar in artesunate–amodiaquine and artemether–lumefantrine-treated patients: $4.8 \pm 1.9\%$ (range 2–9) vs $4.4 \pm 2.4\%$ (range 1–9). FIH/1000 parasites cpb was significantly lower in hyperparasitemic than in non-hyperparasitemic children (0.01 ± 0.007 vs $0.12 \pm 0.15\%$, $p < 0.001$) (Fig. 1). Haematocrit conservation ratio was 12. Overall, declines of parasitemias was monoexponential; estimated mean half-life ($t_{1/2el}$): 1.0 ± 0.11 h (SEM) (range 0.64–2.1) and 1.2 ± 0.66 (SEM) (range 0.64–2.2) in hyperparasitaemic and non-hyperparasitaemic children, respectively (Fig. 2). The estimated mean $t_{1/2el}$ were similar in hyperparasitaemic children treated with artesunate–amodiaquine [0.98 ± 0.16 h (SEM), range 0.64–2.1, $n = 11$] or artemether–lumefantrine [1.0 ± 0.2 h (SEM), range 0.64–2.1, $n = 15$].

TABLE 1
Characteristics of hyperparasitaemic children

Variable	Artesunate–amodiaquine ($n = 24$)	Artemether–lumefantrine ($n = 32$)
M:F	14:10	18:14
Age (years)	6.2 ± 3.3	6.0 ± 3.1
Range	2–12	0.87–12
Body temperature (°C)	38.1 ± 1.4	38.1 ± 1.2
Range	36.1–41.1	36.1–40.5
Haematocrit (%)	33.1 ± 5.3	32.7 ± 4.2
Range	24–41	21–40
No. <30%	6	3
Duration of illness (days)	2.3 ± 1.0	3.0 ± 1.4
GMPD (per µl blood)	546 147	366 011
Range	258 823–2 124 000	251 142–1 125 000*

GMPD, geometric mean parasite density. *$p = 0.03$.

Discussion

Both artesunate–amodiaquine and artemether–lumefantrine were effective treatment of uncomplicated *Pf*HP. Ethical justification for treatment of the children was based on the absence of other symptoms and signs of severe malaria, oral fluid and drug tolerance and known rapid parasiticidal effects of Artemisinin based combination therapies (ACT) and close monitoring. Artesunate may significantly increase the number of circulating red cell surface antigen (RESA)-positive parasite-negative red cells [6], producing a lesser than expected FIH if all infected erythrocytes were to be destroyed following treatment. Standardizing FIH by relating it to 1000 parasites cleared from the peripheral blood after ACT treatment showed significantly lower fall in hyperparasitaemic compared with non-hyperparasitaemic children, suggesting haematocrit conservation in hyperparasitaemia following ACT use. The parasitaemia half-life of 1 h provides a baseline for which future changes in parasite population *in vivo* and *in vitro* susceptibility profiles from this endemic area may be compared. As resistance to

TABLE 2
Therapeutic responses to artesunate-amodiaquine or artemether-lumefantrine

Variable	Amodiaquine–artesunate	Artemether–lumefantrine
Fever clearance time (days)		
Mean ± SD	1.07 ± 0.26 ($n = 14$)	1.1 ± 0.3 ($n = 20$)
Range	1–2	1–2
Parasite clearance time (days)		
Mean ± SD	0.98 ± 0.43	1.6 ± 0.56
Range	1–2	1–2
Day and responses (S/RI/RII)		
28	24/0/	31/1/
35	24/0/	31/1/
42	23/1/	26/6/
ACPR	23	28
LPF	1	6
LCF	0	4
ETF	0	0
Cure rate (%)	95.8	81.2

ACPR, adequate clinical and parasitological response; LPF, late parasitological failure; LCF, late clinical failure; ETF, early treatment failure; S, sensitive; R, resistant.

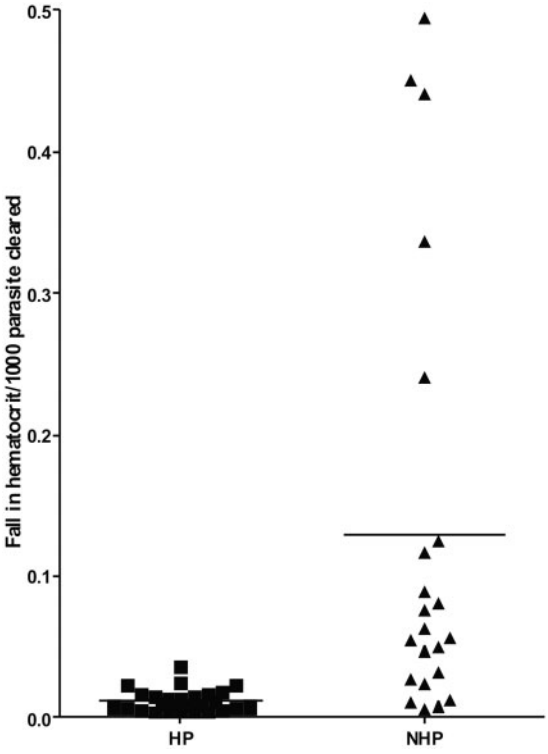

FIG. 1. Fall in hematocrit per 1000 parasites cleared from peripheral blood in children with hyperparasitaemia (HP) and in age- and gender-matched children without hyperparasitaemia (NHP) after treatment of falciparum infections with artesunate–amodiaquine or artemether–lumefantrine.

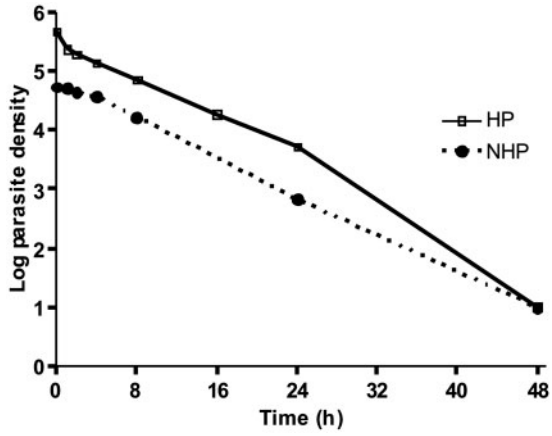

FIG. 2. Semi-log plots of parasitemia versus time in children with hyperparasitaemia (HP, solid line) and in age- and gender-matched children without hyperparasitaemia (NHP, broken line) after treatment of falciparum infections with artesunate–amodiaquine or artemether–lumefantrine).

ACT develops, parasitaemia half-life will be expected to increase.

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