A Simple Dose Regimen of Artesunate and Amodiaquine Based on Arm Span- or Age Range for Childhood Falciparum Malaria: A Preliminary Evaluation

by Akintunde Sowunmi,[1,2] Ibukun A. Akinrinola,[1] Grace O. Gbotosho,[1,2] Titilope M. Okuboyejo,[1] *and* Christian T. Happi[1,2]
[1]*Department of Pharmacology and Therapeutics, University of Ibadan, Ibadan, Nigeria*
[2]*Institute for Medical Research Training, University of Ibadan, Ibadan, Nigeria*

Correspondence: Akintunde Sowunmi, Department of Clinical Pharmacology, University College Hospital, Ibadan, Nigeria. Tel: +234-802-3359-390; E-mail: <akinsowunmi@hotmail.com>.

Summary

A dose regimen of artesunate and amodiaquine based on arm span- or age range (DRAAAS), derived from a study of 1674 children, was compared with standard dose regimen of the same drugs calculated according to body weight (SDRAA) in 68 malarious children. Children on DRAAAS received 0.8–1.0 of artesunate/kg and 0.9–1.2 times amodiaquine/kg compared with those receiving SDRAA. Parasite and fever clearance and fall in hematocrit in the first 3 days were similar; both regimens were well tolerated. DRAAAS is simple and is efficacious.

Key words: dose regimen, arm span, anti-malarials, children.

Introduction

Artemisinin combination therapies are the recommended first-line treatment of *Plasmodium falciparum* malaria globally [1]; their dose regimens have been calculated according to body weight, that is, mg kg^{-1} or on weight- or age range. In many malaria endemic communities, body weight cannot be readily measured because of lack of or non-functional weighing scales. Alternatives to weight-based dose regimens are needed in these communities. Arm span is related to height and body weight [2], can be readily measured in physically challenged or young children. However, it has not been explored in designing dose regimens of anti-malarial drugs. We measured arm span, developed dose regimen based on the measurement in children and compared the therapeutic efficacy of artesunate and amodiaquine using dose regimen based on arm span with the standard dose regimen of these drugs calculated according to body weight in malarious children.

Patients and Methods

The study was done in Ibadan, Nigeria from February 2010 to March 2011 and was in two parts (Fig. 1). Demographic characteristics, height, arm span and body weight were recorded in 1674 ≤15-years olds and, height for age, arm span for age, body weight for age, height for arm span, body weight for height and body weight for arm span data were generated. The children were grouped into four categories (Table 1). In all categories, arm span correlated with age ($r > 0.58$ and $p < 0.0001$ in all cases).

Predefined characteristics of the dose regimen are as follows: maximum of four arm span or age categories; doubling of dose from minimum arm span or age category (Category I) to the next age or arm span category (Category II); doubling in dose to the next arm span or age category (Category III); 50% increase in dose from Category III to the highest arm span or age category (Category IV); no splitting of tablets for Categories II–IV.

The dose regimen based on arm span or age range was modeled in a manner similar to the age- or weight-range currently used for artemether–lumefantrine. Table 1 shows the dose regimens adopted.

Criteria for selection to efficacy of the two regimens are as follows: age ≤15 years; symptoms compatible of acute uncomplicated malaria; *Plasmodium falciparum* parasitemia >2000 asexual forms/μl, body temperature >37.4°C or history of fever in the 24–48 h preceding presentation; absence of other concomitant illness; no history of anti-malarial drug use in the 2 weeks preceding presentation, and written informed consent given by parents or guardian. Patients with severe malaria, severe malnutrition, serious underlying diseases and known allergy to study drugs were excluded. Ethical approval was granted

doi:10.1093/tropej/fmr091 Advance Access published on 3 November 2011

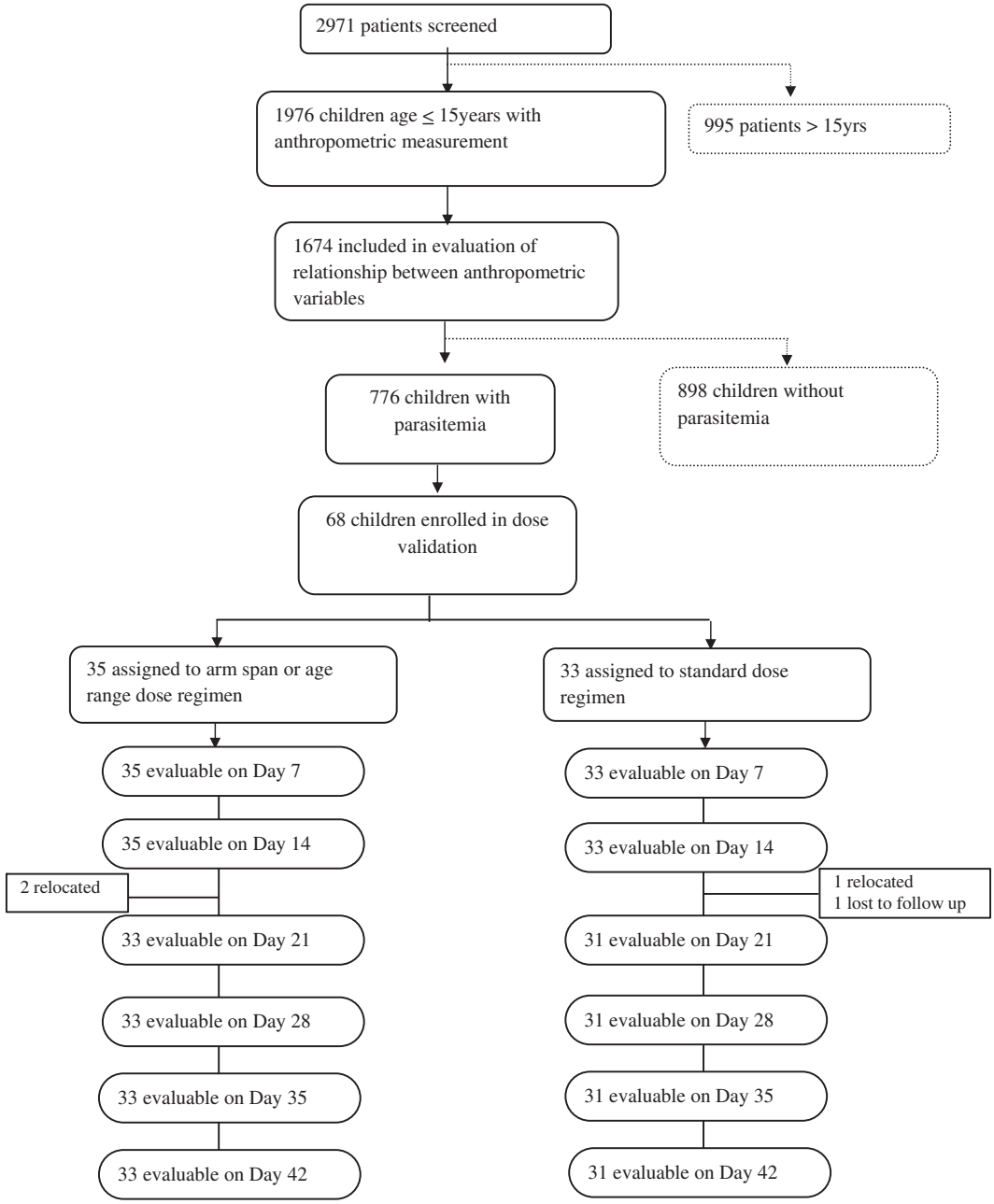

FIG. 1. Study profile.

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 drug regimen of Artesunate and Amodiaquine based on arm span- or age –range (DRAAAS) or standard dose regimen of artesunate and amodiaquine (SDRAA). Patients in DRAAAS group received artesunate and amodiaquine co-packaged according to age or arm span range as follows: children aged 0.5–1 years or 60–75 cm arm span width received half tablet each of amodiaquine and artesuante; children aged

TABLE 1
Category and dose regimen adopted and the number of children who were under- or over-dosed by standard dose regimen

Category and arm span or age range	No. of tablets over 3 days	No. receiving AS <12 mg/kg AQ <30 mg/kg	No. receiving AS 12 mg/kg AQ 30 mg/kg	No. receiving AS >12 mg/kg AQ >30 mg/kg
I 60–75 cm [67 ± 4.0] (2–21/2 rulers) or 6 months–1 year [0.69 ± 0.1] *n* = 0	$1^1/_2$ AS = 75 mg $1^1/_2$ AQ = 229.5 mg	0	0	0
II 76–120 cm [93.8 ± 12.6] (>21/2–4 rulers) or >1–5 years [3.4 ± 1.2] *n* = 13	3 AS = 150 mg 3 AQ = 459 mg	3	6	4
III 121–140 cm [121.3 ± 11.9] (>4–$4^2/_3$ rulers) or >5–10 years [7.8 ± 1.5] *n* = 15	6 AS = 300 mg 6 AQ = 918 mg	1	4	10
IV 141–165 cm [145 ± 10] (> $4^2/_3$ rulers–5 ½) or >10–15 years [12,5 ± 1.3] *n* = 7	9 AS = 450 mg 9 AQ = 1377 mg	0	0	7

AS, artesunate; AQ, amodiaquine; 1 ruler = 30 cm/12.5 inches.

>1–5 years or 76–120 cm arm span width received one tablet each of amodiaquine and artesunate; >5–10 years or 121–140 cm arm span width received two tablets each of amodiaquine and artesunate; 11–15 years or 140–165 cm arm span width received three tablets each of amodiaquine and artesunate daily for 3 days. Each tablet of amodiaquine contains 153 mg base and each tablet of artesunate 50 mg (Table 1). Patients assigned to SDRAA received artesunate–amodiaquine co-packaged according to body weight given as follows: 4 mg kg^{-1} artesunate and 10 mg/kg amodiaquine base daily for 3 days.

Paracetamol tablets, 10–15 mg kg^{-1} were given every 8 h for 24 h. Follow-up (clinical and parasitological) was carried out daily on days 1–7, 14, 21, 28, 35 and 42 after treatment. Response to treatment, parasite and fever clearance times were as previously described [3]. Cure rate were the percentages of patients whose asexual parasitaemia cleared from peripheral blood and who were free of parasitaemia on days 14–42.

Thick and thin blood films prepared from a finger prick were Giemsa stained and examined by light microscopy. Asexual parasitemia in thick films was estimated by counting asexual forms relative to 500 leucocytes and the parasite density was calculated assuming a leucocyte count of 6000/μl of blood [4]. Routine hematocrit was done on days 0–7, 14, 21, 28, 35 and 42. Drug-attributable fall in hematocrit (DAFH) during treatment was defined as the difference between patient's hematocrit on day 0 and day 3 after starting treatment [5]. Area under the curve of deficit in hematocrit (AUC_{def}) was calculated as previously described [3].

Sample size was calculated so that the study would be able to detect a 21% absolute difference in parasitological failure rate, between DRAAAS and SDRAA groups with 80% power and at a 5% significance level. The expected treatment success rates were 100% for SDRAA and 79% for DRAAAS on day 28–42. The minimum sample size in each treatment arm was 32. Data were analyzed using the statistical program *SPSS for Windows* version 15.0 [6].

Results

Dose categories of DRAAAS and the proportions of children who received below (11.8%), above (62.7%) or ~12 mg kg^{-1} of artesunate and 30 mg kg^{-1} of amodiaquine (25.5%) are summarized in Table 1. All children recovered clinically within 2 days. In both groups, enrolment parameters were similar (Table 2), as were the therapeutic responses (Table 3). Gametocytemia cleared in all children by 1 week of

TABLE 2
Characteristics of malarious children

	DRAAAS	SDRAA
No. of patients		
Male/female	35	33
No. <5 years	16/19	16/17
	11	8
Age (year), mean ± SD		
Range	7.1 [±3.4]	7.5 [±3.7]
	1.9–14	0.5–14
Weight (kg), mean ± SD	21.2 [±7.8]	21.7 [±8.7]
Range	12–40	8–39
Height (cm), mean ± SD	117.2 [±20.3]	118.6 [±20.9]
Range	85–156	62–156
Arm span (cm), mean ± SD	117.9 [±20.9]	118.9 [±25.4]
Range	84–156	63–163
Hematocrit (%), mean ± SD	32.2 ± 4.8	33.8 ± 3.79
Range	23–43	27–42
<30%	10	3
Temperature (°C), mean ± SD	38.8 ± 4.5	38.6 ± 1.1
Range	36.8–40.9	36.6–40.3
Duration of illness (days), mean ± SD	3.3 ± 1.3	3.0 ± 1.1
Range	1–28	1–7
Pulse rate (/min) (mean[SD])	122.1 ± 26.5	126.5 ± 31.7
Range	64–192	72–196
Respiration rate (/min), mean ± SD	33.8 [10.6]	38.1 [14.2]
Range	18–75	20–73
GMPD (/μl blood)	69 787	46 529
Range	2924–448 204	3529–10 80 200
>250 000	4	2
Gametocytemia	3	4

Values are mean ± SD, range. GMPD, geometric mean parasite density;

TABLE 3
Therapeutic responses to arm span- or age range or standard dose regimen of artesunate and amodiaquine

	DRAAAS	SDRAA	*p* value
—Fever clearance time (days)			
Mean ± SD	1.1 ± 0.3 (n = 29)	1.1 ± 0.3 (n = 31)	-
Range	1–2	1–2	
95% CI	1.0–1.2	1.0–1.2	
No. of patients with parasitemia on Day 1	4	3	0.89
—Time to clear 50% parasitemia (days)			
Mean ± SD	0.6 ± 0.1	0.5 ± 0.1	0.76
Range	0.5–1	0.5–1	
95% CI	0.5–0.6	0.5–0.6	
—Time to clear 90% parasitemia (days)			
Mean ± SD	1.0 ± 0.3	1.0 ± 0.3	0.76
Range	1–1.8	1–2	
95% CI	1.0–1.1	1.0–1.1	
—Parasite clearance time (days)			
Mean ± SD	1.1 ± 0.3	1.1 ± 0.3	0.76
Range	1–2	1–2	
95% CI	1–1.2	1.0–1.2	
—Day and responses (S/RI/RII)			
14	35/0/0	33/0/0	
21	33/0/	31/0/	
28	33/0/	31/0/	
35	33/0/	31/0/	
42	33/0/	30/1/	
ACPR	33	30	0.98
LPF	0	1	
LCF	0	0	
ETF	0	0	
PCR-uncorrected cure rate (%)	100	96.7	0.95

PCR, polymerase chain reaction
ACPR, adequate clinical and parasitological response; LPF, late parasitological failure; LCF, late clinical failure; ETF, early treatment failure.

commencing treatment. Overall, 17 and 19 in the DRAAAS and SDRAA groups, respectively, reported at least one adverse event; the most frequent were cough and fever cough in both treatment arms.

The proportions of children with a fall in hematocrit on Day 3 were similar (8 of 34 children in DRAAAS vs 3 of 33 children in SDRAA, $p = 0.21$; DAFH were 3.6 ± 2.9, vs 3.7 ± 2.3%, respectively, $p = 0.87$, Fig. 2). The rates of rise in hematocrit were similar such that by day 28 there were no further increases in hematocrit values with both regimens (Fig. 2).

Mean AUC_{def} in the two regimens. Mean AUC_{def} in DRAAAS ans SDRAA was similar (26.2 ± 10.7 [SEM], range 1.2–112.4 vs 16.3 ± 8.3, range 0.3–28.1%.h, $p = 0.36$) (Figure 3).

Discussion

There is increasing need for alternative anthropometric methods apart from weight, age or height for designing dose regimens in resource poor malaria endemic countries. Arm span measurement is one alternative. The advantages of arm span-based regimen over weight based methods are: no requirement for weighing scale, use in physically challenged or young children unable to stand, little or no body exposure during measurement and no requirement for removing clothing.

Both regimens were efficacious treatment of malaria and were well tolerated despite over half of the children in the arm-spam based regimen receiving greater than the required dose calculated according to body weight. The favorable clinical and

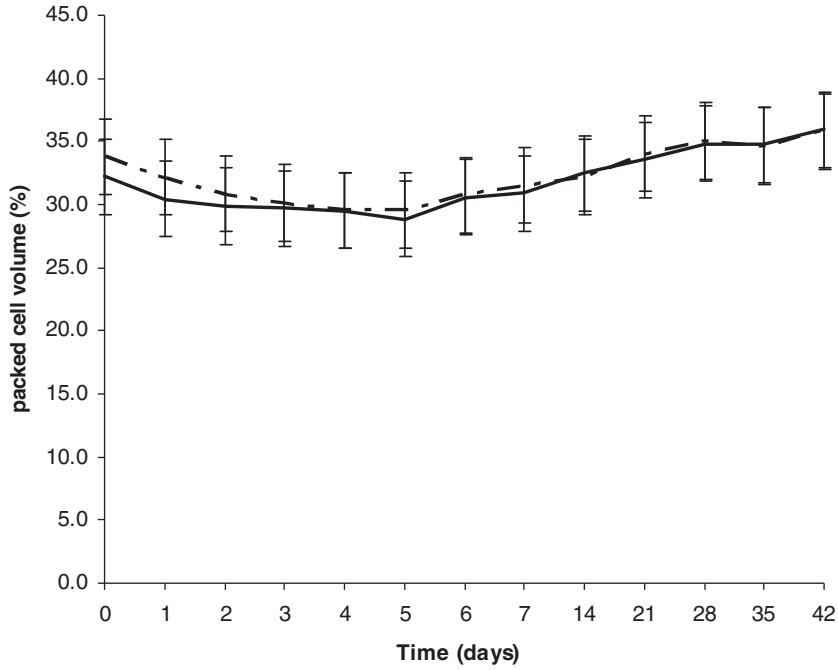

FIG. 2. Changes in hematocrit before, during and after treatment with arm span or age range dose regimen of artesunate and amodiaquine (solid line) and standard dose regimen of artesunate and amodiaquine (broken line) in malarious children.

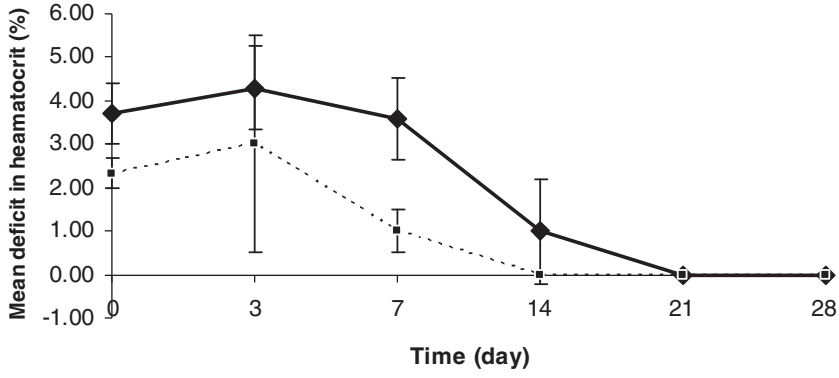

FIG. 3. Area under curve of mean deficit in hematocrit in patients treated with arm span based dose regimen (solid line) or standard dose regimen (broken line).

parasitological efficacy of DRAAAS, on the whole, appears similar to those of other studies employing loose combination or co-formulation of artesunate and amodiaquine [3]. The main drawback of using arm span to design dose regimen is a tendency to reduce routine taking of children's weight with a reduced tendency to detect acute malnutrition in individual children and in communities. In conclusion arm span or age-range dose regimen of artesunate and amodiaquine is simple and efficacious. The regimen requires further evaluation in larger and longer field studies.

References

1. World Health Organization. Antimalarial drug combination therapy- Report of a WHO Technical

Consultation. In: Geyer M (ed.). Geneva: Roll Back Malaria, World Health Organization, 2001.
2. Yabanci N, Kiliç S, Simsek I. The relationship between height and arm span, mid-upper arm and waist circumferences in children. Ann human Biol 2010;37:70–75.
3. Gbotosho GO, Sowunmi A, Okuboyejo TM, *et al.* Therapeutic efficacy and effects of artemether-lumefantrine and artesunate-amodiaquine co-formulated or co-packaged, on malaria-associated anemia in children with uncomplicated *Plasmodium falciparum* malaria in southwest Nigeria. Am J Trop Med Hyg 2011;84:813–9.
4. Sowunmi A, Akindele JA, Balogun MA. Leukocyte counts in falciparum malaria in African children from an endemic area. Afr J Med Sci 1995;24:145–9.
5. Sowunmi A, Balogun ST, Gbotosho GO, *et al.* Effects of amodiaquine, artesunate, and artesunate-amodiaquine on *Plasmodium falciparum* malaria-associated anaemia in children. Acta Tropica 2009; 109:55–60.
6. Anonymous. SPSS for Windows release 15.0.0 Chicago, IL: SPSS Inc, 2006.