Use of weight-for-age-data to optimize tablet strength and dosing regimens for a new fixed-dose artesunate-amodiaquine combination for treating falciparum malaria

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Objective To test a novel methodology to define age-based dosing regimens for the treatment of malaria with a new, user-friendly, blister-packaged fixed-dose combination of artesunate and amodiaquine.

Methods A weight-for-age reference database of 88 054 individuals from sub-Saharan Africa was compiled using data from Demographic Health Surveys, observational and intervention studies, and standardized for sex, age and malaria risk. We then determined the optimal tablet strength (milligram (mg) per tablet) and age–dose categories for the combination of artesunate and amodiaquine. The proportions of patients predicted to receive doses within newly defined therapeutic ranges for amodiaquine (7–15 mg/kg/day) and artesunate (2–10 mg/kg/day), were estimated for different age categories and mg tablet strengths using models based on the weight-for-age reference database.

Findings The optimal paediatric (p) and adult (a) strength tablets contained 25/67.5 and 100/270 mg artesunate/amodiaquine, respectively. A regimen with five age categories: 0–1 months (½ p), 2–11 months (1 p), 1–5 years (2 p), 6–13 years (1 a), and ⩾ 14 years (2 a) had an overall dosing accuracy of 83.4% and 99.9% for amodiaquine and artesunate, respectively.

Conclusion The proposed method to use weight-for-age reference data from countries where malaria is endemic is a useful tool for designing age-based dosing regimens for antimalarial drugs for drug registration and field use.

Bulletin of the World Health Organization 2006;84:956-964.

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يمكن الاطلاع على الملخص بالعربية في صفحة 963.

Introduction

Rapid access to diagnosis and effective treatment is essential in the drive to roll back malaria.[1] Following the results of multicentre, proof of principle, clinical trials of artesunate combined with standard antimalarials, WHO now recommends artemisinin-based combination therapy (ACTs) as first-line treatment for *Plasmodium falciparum* malaria.[2–5] Four ACTs are currently recommended: artesunate (AS) combined with mefloquine, amodiaquine (AQ) or sulfadoxine–pyrimethamine, and artemether–lumefantrine. Some 42 malaria endemic countries have now adopted or registered ACTs.[1]

Practical, user-friendly drug regimens should improve patient adherence, dosing accuracy, and, consequently, drug safety, effectiveness, and acceptability.[6] User-friendliness can be improved by blister packaging and the use of fixed-dose combination tablets.[7–10] Fixed-dose combinations avoid the risk of single-drug intake,[11] ensure maximum parasiticidal effects and reduce the risk of the development of de novo resistant parasites.[12] Artemether–lumefantrine is currently the only internationally registered, fixed-dose, artemisinin-based combination in use, but other fixed-dose combinations are being developed (e.g. AS plus amodiaquine, mefloquine, pyronaridine, chlorproguanil–dapsone, and dihydroartemisinin plus piperaquine).

In standard regulatory clinical trials for drug registration, drug doses are typically calculated according to body weight i.e. on a milligram per kilogram (mg per kg) basis. However, weight-based dosing in countries where malaria is endemic is challenging because functioning weighing scales are scarce, access to formal health services is limited and most treatment occurs at home using antimalarials bought from shops and street vendors.[13–16] Therefore, by default, the doses of most malaria treatments are administered by age. Cogniscent of this practice, WHO has produced both age- and weight-based recommendations for the commonly used antimalarial drugs.[17] Age-based dosing is more practical than weight-based dosing, but inevitably results in some children receiving drug dosages, in mg per kg body weight, below and above those recommended, with the attendant risks of treatment failure or toxicity.

Here, we report the use of a new methodology using weight-for-age reference data from countries where malaria

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Ref. no. **06-031492**

(*Submitted: 10 March 2006 – Final revised version received: 20 May 2006 – Accepted: 24 May 2006*)

is endemic, to determine the optimal tablet strength (i.e. the amount of drug in mg per tablet) and corresponding age-based dosing regimens for a new blister-packaged fixed-dose combination of AS and AQ.

Methods

Our aim was to design a practical age-based dosing regimen that minimized the number of age categories and maximized the proportions of patients predicted to receive doses of AQ and AS within newly defined therapeutic ranges. We used computer models to compare the proportion of patients who were predicted to receive dosages within the recommended ranges with different tablet strengths of AQ and AS and different age categories using anthropometric reference data from countries in sub-Saharan Africa where malaria is endemic.

Definitions of adequate therapeutic dose margins

We defined therapeutic dose ranges for AS and AQ using current dosing recommendations, published and unpublished data, and anecdotal clinical experience of their efficacy and tolerability. Dosing outside these limits was defined as either an underdose or overdose.

Amodiaquine

The 4-aminoquinoline AQ is a well established antimalarial that is administered at doses of 25 or 30 mg/kg base over 3 days;[18,19] WHO now recommends the higher dose.[2,17,20] The efficacy of AS and AQ depends on the degree of resistance to AQ.[2,3] In Kenya a 28-day cure rate of only 68% was found,[2] but in southern Senegal, the efficacy of 3 days of treatment with co-blistered loose tablets of AS and AQ (Arsucam, Sanofi Aventis, France) was 95%.[21] The therapeutic range in Senegal was 7.5–15 mg/kg AQ per day (i.e. 22.5–45 mg/kg over 3 days).

As prophylaxis (400 mg weekly in adults), AQ has caused severe neutropenia (estimated risk 1/2000) and hepatitis (1/15650), both of which are potentially fatal.[22,23] The main mechanism is probably a type II hypersensitivity reaction to a quinone imine metabolite, but direct drug toxicity against bone marrow precursors of white blood cells and hepatocytes can not be excluded.[24–27]

When used as treatment, at a dosage according to weight or age, AQ alone or combined with AS is well tolerated.[28] The reported rates of drug-induced vomiting, requiring a change of treatment (< 1.2%) and pruritus (< 1 to 2%), are low.[2,21] Total AQ doses of 15–50 (median 31.3) mg/kg were well tolerated in 397 west Africans of all ages.[29] However, clinical experience from Cameroon found vomiting to be troublesome in schoolchildren aged 5–15 years given an initial dose of 15 mg/kg of AQ. Consequently, this dose was replaced with 10 mg/kg with good results (P Ringwald, personal communication). Severe, asymptomatic neutropenia (< 1000/μl) was reported on day 28 in 9 of 152 (6%) children infected with *P. falciparum* when treated with AQ alone (total dose 30 mg/kg) or in combination with AS.[2]

Based on these data, the therapeutic dose for AQ was set at 7.5–15 mg/kg/day (i.e. 22.5–45 mg/kg over 3 days).

Artesunate

The currently recommended target dosage for AS is 4 mg/kg daily for 3 days. A dose-finding study in Thailand found that 2 mg/kg/day of AS, when combined with mefloquine, was the lowest dose that achieved a maximum parasiticidal effect.[30] The currently recommended dose of 4 mg/kg/day takes into account the wide variation of AS concentrations between individual malaria patients, and so reduces the probability of underdosing.[31] This dose of AS, combined with mefloquine, has achieved consistently high cure rates of more than 95% since 1995 on the western border of Thailand, an area with highly multidrug resistant *P. falciparum*.[32]

As a class, the artemisinin compounds are remarkably well tolerated.[28,33–36] Serious, AS-induced toxicity is confined to acute anaphylaxis which has an estimated risk of 1 in 2833.[34–37] Acute intravascular haemolysis has been described following treatment with AS, artemether and other antimalarials and is probably malaria-related.[31,38–40] The tolerability of AS in combination with other antimalarial drugs is essentially that of the partner drug.[3,41] One study (n = 211) used a stat dose (a single dose given at one time-point) of 10 mg/kg of AS with mefloquine which was better tolerated than mefloquine alone; no adverse effects were associated with this dose of AS.[42]

On the basis of these published data, the therapeutic dose for AS was defined as 2–10 mg/kg/day (i.e. 6–30 mg/kg over 3 days).

Weight-for-age reference population database

The WHO/National Centre for Health Statistics (WHO/NCHS) weight-for-age reference data are based on well nourished populations from developed countries and are appropriate for comparing the nutritional status of different populations.[43] Our analysis required anthropometric data from the target population itself. Therefore, a weight-for-age data set (n = 88 054) was created from individuals from countries in sub-Saharan Africa where malaria is endemic. Reference data for African children < 5 years (y) of age from 21 countries were compiled from Demographic Health Surveys (DHS) with permission from the Measure-DHS web site (http://www.measuredhs.com).[44] The remaining data (on children aged ⩾ 5 years) were provided by investigators from six different nutritional surveys and other studies involving nutritional assessment in schoolchildren and adults

Table 1. **Predefined characteristics of the drug regimen**

Characteristic	Description
Age categories	Maximum of 5 age categories: 2 in infants and 3 in older children, adolescents and adults (⩾ 14 years). Use of full-month (integer) age cut-off points for infants and full-year age cut-off points only in older children[a]
Tablet characteristics	One paediatric and one adult tablet strength formulation in a mg ratio of 1:4 for each drug
Number of tablets	Maximum of two per age category
Tablet fraction	Only in infants aged < 2 months
Dose/age category[b]	Doubling of the mg/dose: ½ p, 1 p, 2 p, 1 a and 2 a

[a] e.g. 2 months, not 2.4 months; 10 years not 9.6 years.
[b] p = Paediatric-strength tablet; a = adult-strength tablet.

from Ghana, Kenya, Mozambique and the United Republic of Tanzania.

This data set was standardized by age and sex, so that there was equal sex distribution in each 1-year age category and the age distribution was typical of a sub-Saharan African population, based on demographic tables published by WHO.[45] In this standardized data set, 29.5% of the children aged < 5 years were classified as underweight according to the NCHS/WHO reference. The mean (standard deviation) weight-for-age Z-score was –1.30 (0.59).

The analysis was also standardized (weighted) for malaria risk, taking into account that the risk of clinical malaria varies with age in sub-Saharan Africa. We used a weighting factor of 3 for children aged 0–11 months, 4 for children 1–3 years, 3 for children 4–5 years, 2 for children 6–7 years and 1.5 for children 8–11 years relative to categories for older children and adults which were given a weighting factor of 1. The weighting factors used were considered representative of the average age pattern for clinical malaria in malaria-endemic countries in Africa. This final data set, i.e. standardized for age, sex and malaria risk is referred to as the malaria-weighted anthropometric reference (MWAR) data set.

Determining the optimal tablet strength and age categories

We followed the convention of doubling the drug dose per age category and selected five age groups which had an approximate doubling in median bodyweight: 0–1 months (4.2 kg), 2–11 months (6.9 kg), 1–6 years (13.3 kg), 7–13 years (25.6 kg), and ⩾ 14 years (58.0 kg). Based on our predefined dosing criteria (Table 1), the corresponding doses were ½, 1, and 2 paediatric tablets, and 1 and 2 adult-strength tablets, respectively. These default age and dose groups were used to determine optimal tablet strengths.

The optimal tablet strengths defined in the initial model were subsequently used to see if dosing accuracy could be improved by using age categories different to the default categories described above.

Weight-for-age reference data in a healthy population versus malaria patients

The MWAR data from children < 5 years were compiled using DHS data obtained from random samples of predominantly healthy children as part of cross-sectional surveys. Few of these children would have had acute malaria at the time of the survey. To assess whether the use of the MWAR data set was appropriate for designing treatment regimens for sick children with acute malaria, we also defined the optimal regimen using a data set of 27 255 Mozambican children aged < 5 years with clinical malaria who attended outpatient clinics (Alonso et al., unpublished data). The results were compared with those based on the MWAR data.

Dosing by body weight

To compare the performance of the age-based regimen with that of a weight-based regimen, the MWAR data set was used to determine optimal weight categories based on the new tablet strengths and predefined dose categories.

Table 2. **The overall proportions of patients predicted to receive dosages within and outside the defined therapeutic doses of amodiaquine and artesunate using different tablet strengths for both drugs and anthropometric data from sub-Saharan Africa**[a]

Amodiaquine tablet strengths (mg)		Therapeutic dose 7.5–15 mg/kg/day		
Paediatric tablets	Adult tablets	Below (%)	Within (%)	Above (%)
62.5	250	17.6	77.4	5.1
65	260	13.5	79.9	6.6
67.5	270	10.0	81.9	8.2
70	280	8.4	81.1	10.5
72.5	290	5.5	81.8	12.7
75	300	4.1	81.3	14.6
77.5	310	3.4	78.8	17.9
Artesunate tablet strengths (mg)		**Therapeutic dose 2–10 mg/kg/day**		
Paediatric tablets	Adult tablets	Below (%)	Within (%)	Above (%)
20	80	4.1	95.9	0
22.5	90	1.7	98.3	0
25	100	0.1	99.9	0.01
27.5	110	0.06	99.9	0.03
30	120	< 0.01	99.9	0.1
32.5	130	< 0.01	99.5	0.5
35	140	0	99.0	1.0

[a] To obtain the range in mg that needed to be tested we first obtained a crude estimate of the optimal tablet strength by multiplying the median weights for each age category by the currently recommended doses of 10 mg/kg/day for amodiaquine and 4 mg/kg/day for artesunate. This suggests that the optimal paediatric and adult tablet strengths for amodiaquine lay between 67 and 69 mg and between 260 and 290 mg base, respectively. Corresponding values for artesunate were between 26 and 29 mg and between 102 and 116 mg. Dosing accuracy was then compared for several candidate tablet strengths for amodiaquine ranging from 62.5 to 77.5 mg (with increments of 2.5 mg) for the paediatric strength tablet and 250 to 310 mg for the adult strength tablet (with increments of 10 mg). Corresponding candidates for the paediatric and adult tablet strengths for artesunate ranged from 20 to 35 mg (with 2.5 mg increments) and 80 to 140 mg, respectively (with increments of 10 mg). Dosing accuracy was defined as the proportion of individuals (using the MWAR data set) who were predicted to receive a dose within the therapeutic ranges when dose was based on age using the default age categories described above.

Results

Optimal tablet strengths

The proportions of patients predicted to receive therapeutic doses for various tablet strengths of AQ and AS using the five default age categories are shown in Table 2. The differences in these predicted proportions of patients who will receive therapeutic doses, between AQ tablets containing between 67.5 and 75 mg (paediatric strength) and between 270 and 300 mg (adult strength) were negligible. Artesunate tablets containing between 25 and 30 mg (paediatric strength) and between 100 and 120 mg (adult strength) would each result in 99.9 per cent of patients receiving doses within the range 2–10 mg/kg/day. We chose the tablets containing 67.5 and 270 mg of AQ and 25 and 100 mg of AS because they were associated with the lowest risk of overdosing.

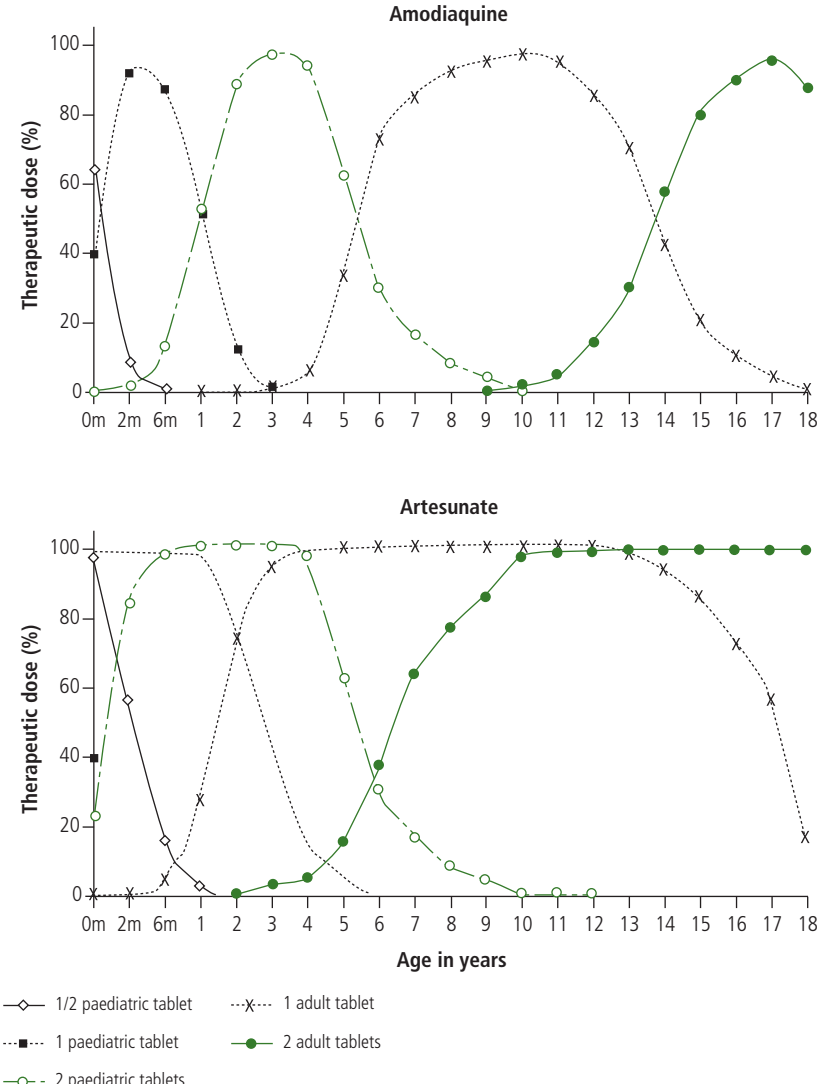
Optimal age categories

Subsequent models were run using the chosen tablet strengths (25/67.5 and 100/270 mg AS/AQ) with various age cut-off points (Table 3; web version only, http://www.who.int/bulletin). This showed that for the step increase from 2 paediatric tablets to 1 adult tablet, an age cut-off point of 6 rather than 7 years would improve the accuracy for AQ. All other optimal age cut-off points were similar to the default cut-off points used in the first model. For AS, dosing accuracy was very insensitive to changes in age cut-off points, in contrast to that for AQ (Fig. 1). Models run with 8 mg/kg as the upper cut-off point for AS provided the same age-cut off points as the models that used 10 mg/kg as the upper threshold (data not shown).

With this new, optimal five-category age-based regimen, the overall proportions of patients predicted to receive dosages within, below and above the therapeutic dose range were 83.4%, 7.4% and 9.1% for AQ, and 99.9%, 0.07% and < 0.01% for AS, respectively (Table 4). The corresponding median doses were 10.2 mg/kg/day (AQ) and 3.6 mg/kg/day (AS).

Children aged 0–1 month, 12–23 months, 5–7 years and 13–15 years were at the highest risk of underdosing or overdosing with AQ (Table 3; web version only, http://www.who.int/bulletin and Fig. 1). Compared with the five-category age-based regimen, a regimen with seven age categories (3 paediatric tablets for 5–7-year-old children and 1½ adult tablets for 12–15-year-old adolescents) would improve overall dosing accuracy from 83.4% to 87.2% for AQ and from 99.90% to 99.97% for AS. Eight age categories (adding a 2½ adult tablets category for those ⩾ 18 years) would change these values to 89.4% and 99.8%, respectively.

Fig. 1. **Proportions of patients predicted to receive dosages within the therapeutic range for amodiaquine (7.5–15 mg/kg/day) and artesunate (2–10 mg/kg/day) as a function of age and number of paediatric and adult strength tablets containing 67.5/25 and 270/100 mg amodiaquine/artesunate, respectively[a]**



[a] Each line represents the proportions of patients who receive a dose within the therapeutic range with ½, 1 or 2 paediatric tablets, or 1 or 2 adult strength tablets. For example with amodiaquine, at the age of 5 years, 62.5% of children would receive the correct dose with 2 paediatric tablets, but only 33.3% with 1 adult tablet. At the age of 6 years, 30.2% would receive the correct dose with 2 paediatric tablets, but 73.1% with 1 adult tablet. This suggests that the switch from 2 paediatric tablets to 1 adult strength tablet should occur at the age of 6 years.

Healthy reference population versus malaria patients

The proportions predicted to receive a dose within, below or above the therapeutic range for AQ were 85.1%, 3.5% and 11.3%, respectively, with the Mozambique data set versus 81.6%, 3.6% and 14.8%, respectively, with the MWAR data set. The corresponding figures for AS were 99.99% within, 0.01% below and 0% above with the Mozambique data set versus 99.89%, 0.09 and 0.01%, respectively, with the MWAR data set.

Weight-based dosing

With five weight categories, 94.6% and 100% of patients would receive therapeutic doses of AQ and AS, respectively (Table 5).

Discussion

Using available weight-for-age reference data from sub-Saharan Africa, we determined the optimal tablet strength and age-based dosing regimen for a new fixed-dose combination of AS plus AQ by modelling the proportions of patients receiving drug doses that are considered safe and efficacious.

Malaria control programmes need simple dosing regimens. Complicated regimens carry the risk of dosing errors, the effects of which may outweigh the intended advantages of greater accuracy. Therefore, we prioritized user-friendliness, while considering carefully the ramifications of this strategy in terms of safety and efficacy. We minimized the number of age categories and the use of tablet fractions by using paediatric and adult strength tablets with a milligram ratio

Table 4. **The proportions of patients predicted to receive doses below, within and above the therapeutic range using the selected age-based regimen with paediatric and adult strength tablets containing 67.5/25 and 270/100 mg amodiaquine/artesunate**

Amodiaquine			Therapeutic dose 7.5–15 mg/kg/day			Predicted dose received mg/kg/day[a]		
Age group[b]	Dose (tablet)[c]	Dose (mg)	Below (%)	Within (%)	Above (%)	Percentiles		
						1st	50th	99th
0–1 m	½ p	33.8	36.0	63.5	0.4	5.0	8.0	14.1
2–11 m	1 p	67.5	7.4	89.4	3.3	6.3	9.8	17.3
1–5 y	2 p	135	6.5	77.8	15.7	6.3	11.2	20.5
6–13 y	1 a	270	4.2	86.8	9.0	6.4	11.5	19.0
⩾ 14 y	2 a	540	9.2	86.7	4.1	5.7	9.3	18.1
All			7.4	83.4	9.1	5.9	10.2	19.6
Artesunate			**Therapeutic range 2–10 mg/kg/day**			**Predicted dose received mg/kg/day[a]**		
Age group	Dose (tablet)	Dose (mg)	Below (%)	Within (%)	Above (%)	Percentiles		
						1st	50th	99th
0–1 m	½ p	12.5	2.2	97.8	0	1.9	3.0	5.2
2–11 m	1 p	25	0.1	99.9	0.02	2.3	3.6	6.4
1–5 y	2 p	50	0.01	99.98	0.01	2.3	4.1	7.6
6–13 y	1 a	100	0.2	99.8	0	2.4	4.3	7.0
⩾ 14	2 a	200	0	100	0	2.1	3.4	6.7
All			0.07	99.92	0.01	1.5	3.6	7.2

[a] Total dose in mg divided by the median weight (50th percentile) and by the 1st and 99th percentile of the weight within a given age category of the standardized reference anthropometric data set from sub-Saharan Africa.
[b] m = months; y = years.
[c] p = paediatric tablet; a = adult tablet.

of 1:4, restricting dosing to two tablets per dose, and doubling the dose with each increase in dose category. With an average adult weight of between 60 and 70 kg, this translated into a maximum of five age categories.

Determining dosing accuracy demanded a redefinition of acceptable dosing ranges for both drugs. The therapeutic index was wide for AS (5-fold; 2–10 mg/kg/day), reflecting its excellent safety and tolerability. There was less flexibility with AQ (therapeutic index of 2; 7.5–15 mg/kg/day) because it has dose-limited toxicity (15 mg/kg/day), AQ had been reported to cause high rates of vomiting in children (P Ringwald, personal communication). Thus, AQ determined the age cut-off points for each age category. Because the upper limit for AS was based on a single study involving 220 patients from Thailand we also ran the models using a more conservative upper threshold of 8 mg/kg (therapeutic index 4). This did not change the definition of the optimal age cut-off points of the combination, demonstrating again that the drug (AQ) with the lower therapeutic index determines the age categories. Nevertheless, an evaluation of the tolerability of this fixed AS/AQ combination will be necessary in further clinical trials and, when deployed widely, by pharmacovigilance.

The model predicted that virtually all patients in each age category would receive a therapeutic dose of AS with paediatric (25–30 mg) and adult (100–120 mg) tablet strengths. Tablets containing 25 and 100 mg AS were chosen because these carried the lowest risk of overdosing; only 1 in 10 000 recipients would receive > 10 mg/kg/day; 1 in 250 would receive > 8 mg/kg/day; and 1 in 1000 patients < 2 mg/kg/day. The same reasoning applied to the final choice of strength of the AQ tablets (67.5 and 270 mg), resulting in 83.4% of patients predicted to receive a therapeutic dose of AQ.

Two age categories were needed for infants because this is the period of maximum growth rate. Within each age–dosing category, younger and underweight children are at greater risk of overdosing and vice versa. Models with seven or eight age–dosing categories would lead to a modest improvement in overall dosing accuracy (from 83.4% to 87.2% with seven categories and to 89.4% with eight categories) but this would result in greater complexity because tablet fractions, combining paediatric and adult tablets, and more blister-pack sizes would be required. The previous WHO guidelines recommended eight dosing categories for AQ alone (153-mg tablets), with five age categories that require tablet fractions.[17] To our knowledge, adherence to this regimen has not been assessed, but is unlikely to be optimal. To improve dosing accuracy further, dosing by weight is clearly preferable in settings where weighing scales are available, particularly for individuals with extreme weights for age (Table 5).

The anthropometric data for children < 5 years were obtained from large DHS surveys.[44] Use of these household survey data has several important advantages: the methodology is standardized, survey samples are large, nationally representative and available for most sub-Saharan African countries. However, only a small proportion of these children will be acutely ill with malaria at the time of the survey. Malnourished children are more likely to develop clinical malaria, and malaria itself is associated with acute weight loss.[46–48] However, we showed

Table 5. **The proportions of patients predicted to receive dosages below, within and above the therapeutic range using paediatric and adult strength tablets containing 67.5/25 and 270/100 mg amodiaquine/artesunate when dosing by body weight**

Amodiaquine			Therapeutic dose 7.5–15 mg/kg/day[a]			Predicted dose received mg/kg/day		
Weight (kg)[b]	Dose (tablet)[c]	Dose (mg)	Below (%)	Within (%)	Above (%)	Percentiles		
						1st	50th	99th
< 4.5	½ p	33.8	0	99.4	0.6	7.7	8.7	14.1
4.5–8.9	1 p	67.5	0	100	0	7.6	9.3	14.7
9.0–17.9	2 p	135	0	100	0	7.6	10.3	15.0
18.0–35.9	1 a	270	0	100	0	7.6	10.8	14.9
⩾ 36.0	2 a	540	9.4[d]	90.6	0	5.7	9.3	14.7
All			5.4	94.6	0	6.2	9.6	14.8
Artesunate			**Therapeutic dose 2–10 mg/kg/day[a]**			**Predicted dose received mg/kg/day**		
Weight (kg)[b]	Dose (tablet)[c]	Dose (mg)	Below (%)	Within (%)	Above (%)	Percentiles		
						1st	50th	99th
< 4.5	½ p	12.5	0	100	0	2.8	3.2	5.2
4.5–8.9	1 p	25	0	100	0	2.8	3.4	5.4
9.0–17.9	2 p	50	0	100	0	2.8	3.8	5.6
18.0–35.9	1 a	100	0	100	0	2.8	4.0	5.5
⩾ 36.0	2 a	200	0	100	0	2.1	3.5	5.4
All			0	100	0	2.3	3.6	5.5

[a] Total dose in mg divided by the median weight (50th percentile) and by the 1st and 99th percentile of the weight within a given weight category of the standardized reference anthropometric data set from sub-Saharan Africa.

[b] The weight cut-off points for each weight category were determined by dividing the total amodiaquine dose given (No. of tablets × mg content of the amodiaquine tablet) by 15 mg/kg (the upper dose limit). For example, the lower weight limit for children receiving 1 paediatric tablet (67.5 mg) = (1 × 67.5)/15 = 4.5 kg, the lower weight limit of the next dosing group (2 paediatric tablets) = (2 × 67.5)/15 = 9 kg. The optimal lower and upper weight limits for children receiving 1 paediatric tablet are therefore 4.5 to < 9 kg. There were no preset criteria for the minimum weight in the lowest weight group or maximum weight in the highest weight group. Because of the narrower therapeutic index of amodiaquine, the weight categories for this drug were also used for artesunate.

[c] p, paediatric tablet; a, adult strength tablet containing 270/100 mg amodiaquine/artesunate.

[d] Within the group weighing > 36 kg, underdosing with amodiaquine was confined to adults weighing > 72 kg (540 mg per day/72 = 7.5 mg/kg/day). Within the lightest weight group (< 4.5 kg) overdosing (> 15 mg/kg/day of amodiaquine) would occur only if infants weighed < 2.25 kg (33.8 mg per day/22.5 = 15 mg/kg/day).

that the differences between the weight-for-age distributions of children < 5 years of age with acute malaria seeking health care in Mozambique, and randomly selected children enrolled in DHS surveys were small; both data sets produced similar results. This suggests that DHS data are appropriate for defining malaria treatment regimens in young children.

DHS data were not available for older children and other adults. Analyses in these groups were based on much smaller numbers using anthropometric data from individual studies not specifically designed for this purpose. There remains a clear need for more representative data on school-aged children, particularly those aged 5–7 years, and adults, to validate our observations in these older age groups. Furthermore, the dosing regimens presented here were based on African anthropometric data and may not be applicable to other countries. There is an urgent need for similar data sets from other regions where malaria is endemic.

Our methodology does not take into account possible effects of body compositions (e.g. the ratio of lean body mass to body fat), age, gender or ethnicity on the pharmacokinetic and pharmacodynamic characteristics of AQ and AS. However, as with weight-based dosing, it is an approximation of the complex relationship between these parameters and drug safety and efficacy.

To the best of our knowledge, this is the first time modelling with standardized anthropometric reference data from countries where malaria is endemic has been used to define optimal tablet strengths and age-based dosing regimens for treatment of the disease. If field trials confirm the usefulness of this methodology, it could be applied to other drugs for the treatment or prevention of other diseases in the tropics. ■

Acknowledgements

Part of this analysis was funded by a grant from WHO and from the Malaria Knowledge Programme, Liverpool, England. Feiko ter Kuile is grateful to WHO and the US Centers for Disease Control and Prevention (CDC) for financial support. Nicholas J White is a Wellcome Trust Principal Fellow. We thank the following scientists for sharing their data: Dr Pedro Alonso, Dr Simon Brooker, Dr Dennis Shanks, Dr Pascal Magnusson and Dr Jennifer Friedman. We are grateful to Measure DHS for their permission to use the DHS data. The views expressed in this article are those of the authors and not of their institutions.

Competing interests: none declared.

Résumé

Utilisation de données statistiques sur le poids en fonction de l'âge pour optimiser le dosage des comprimés et les schémas posologiques pour une nouvelle association artésunate/amodiaquine en proportions fixes, destinée à traiter le paludisme à falciparum

Objectif Tester une nouvelle méthodologie permettant de définir les schémas posologiques en fonction de l'âge pour le traitement du paludisme par une nouvelle association artésunate/amodiaquine en proportions fixes, conditionnée en plaquettes thermoformées et d'usage facile.

Méthodes Nous avons constitué une base de données de référence sur le poids en fonction de l'âge à partir de données relatives à 88 054 individus, tirées d'Enquêtes Démographiques et de Santé et d'études d'intervention et standardisées pour l'âge, le sexe et le risque de paludisme. Nous avons ensuite déterminé le dosage optimal des comprimés [milligrammes (mg) par comprimé] et les catégories de dose par tranche d'âge pour l'association artésunate/amodiaquine. Pour les différentes tranches d'âge et les différents dosages par comprimé, nous avons élaboré des prévisions estimatives des proportions de malades qui recevront des doses situées dans les plages thérapeutiques nouvellement définies pour l'amodiaquine (7 à 15 mg/kg/j) et l'artésunate (2 à 10 mg/kg/j), à partir de modèles utilisant la base de données de référence pour le poids en fonction de l'âge.

Résultats Les dosages optimaux des comprimés à utiliser en pédiatrie (p) et chez l'adulte (a) pour l'association artésunate/amodiaquine étaient respectivement 25/67,5 et 100/270 mg. Un schéma thérapeutique prévoyant cinq tranches d'âge : 0-1 mois (1/2 p), 2-11 mois (1 p), 1-5 ans (2 p), 6-13 ans (1 a) et ⩾ 14 ans (2 a) présentait une précision posologique globale de 83,4 % pour l'amodiaquine et de 99,9 % pour l'artésunate.

Conclusion La méthode proposée pour exploiter des données de référence sur le poids en fonction de l'âge provenant de pays d'endémie palustre fournit un moyen utile à la définition des schémas posologiques en fonction de l'âge pour des antipaludiques, en vue de l'homologation et de l'usage sur le terrain de ces médicaments.

Resumen

Uso del peso para la edad para optimizar la potencia de los comprimidos y la posología de una nueva combinación de dosis fijas de artesunato-amodiaquina para tratar la malaria por P. falciparum

Objetivo Ensayar una nueva metodología para definir los regímenes de dosificación basados en la edad para el tratamiento de la malaria con una nueva combinación de dosis fijas de artesunato y amodiaquina, fácil de usar y suministrada en forma de blísteres.

Métodos Se compiló una base de datos de referencia del peso para la edad de 88 054 personas del África subsahariana a partir de datos de las Encuestas de Demografía y Salud y estudios observacionales y de intervención, que se normalizaron en función del sexo, la edad y el riesgo de malaria. A partir de ahí se determinó la potencia óptima de los comprimidos (milígramos (mg) por comprimido) y las categorías de edad–dosis para la combinación de artesunato y amodiaquina. Utilizando modelos basados en la base de datos de referencia del peso para la edad, se estimaron, para diferentes categorías de edad y potencias (mg) de los comprimidos, las proporciones de pacientes que recibirían dosis situadas dentro de los márgenes terapéuticos recién definidos para la amodiaquina (7-15 mg/kg/día) y el artesunato (2-10 mg/kg/día).

Resultados La potencia óptima pediátrica (p) y para adultos (a) de los comprimidos fue de 25/67,5 y 100/270 mg de artesunato/amodiaquina, respectivamente. Un régimen basado en cinco categorías de edad (0-1 meses (½ p), 2-11 meses (1 p), 1-5 años (2 p), 6-13 años (1 a), y ⩾ 14 años (2 a)) mostró una precisión de dosificación global del 83,4% y 99,9% para la amodiaquina y el artesunato, respectivamente.

Conclusiones El método propuesto para usar datos de referencia del peso para la edad de los países con malaria endémica constituye una valiosa herramienta para diseñar regímenes de dosificación basados en la edad para los antimaláricos con miras al registro de medicamentos y a su uso sobre el terreno.

ملخص

استخدام معطيات الوزن بالنسبة للعمر للحصول على القوة المثلى للأقراص والمقادير المثلى لجرعات معالجة الملاريا المنجلية بتوليفة جديدة ذات جرعة ثابتة من الأرتيسونات – أموديـاكوين

الهدف: اختبار المنهجية الجديدة لتعريف النُظُم العلاجية المستندة على العمر لمعالجة الملاريا بتوليفة جديدة ذات جرعة ثابتة من الأرتيسونات والأموديـاكومين.

الطريقة: جمِّعت قاعدة معطيات للوزن بالنسبة للعمر ضمت 88 054 فرداً من البلدان الواقعة جنوب الصحراء الأفريقية، باستخدام معطيات من المسوحات الصحية الديمغرافية (السكانية) والدراسات التدخلية ودراسات الملاحظة، مع تعيير (تصحيح) هذه المعطيات بالنسبة للجنس وللعمر ولخطر الملاريا. ثم حدّدنا بعد ذلك القوة المثلى للأقراص (مقدَّرة بميليغرام لكل قرص)، وفئات العمر بالنسبة للجنس المتعلِّقة بتوليفة الأرتيسونات والأموديـاكوين. ثم قدَّرت النسب المئوية للمرضى الذين يتوقع أنهم سيتلقون جرعات ضمن الحدود العلاجية المحددة حديثاً للأموديـاكين (5 – 17 ميلي غرام/كغ/يوم) وللأرتيسونات (2–10 ميلي غرام/كغ/يوم)، وذلك بالنسبة لمختلف فئات العمر ولقوة الأقراص (مقدَّرة بالميليغرامات) وذلك باستخدام نماذج مستندة على قاعدة معطيات مرجعية للوزن بالنسبة للعمر.

الموجودات: تضمَّنت القوة المثلى لأقراص الأطفال 25 ميلغرام من الأرتيسونات و67.5 ميلغرام من الأموديـاكوين، فيما تضمَّنت القوة المثلى لأقراص البالغين 100 ميلغرام من الأرتيسونات و270 ميلي غرام من الأموديـاكوين. إن النظام العلاجي الذي يتضمَّن خمس فئات؛ الفئة الأولى من الولادة إلى عمر شهر (نصف القوة المثلى لأقراص الأطفال)، والفئة الثانية بعمر 2 – 11 شهراً (القوة المثلى لأقراص الأطفال)، والفئة الثالثة بعمر 1 – 5 سنوات (ضعف القوة المثلي لأقراص الأطفال)، والفئة الرابعة بعمر 6 – 13 سنة (القوة المثلى لأقراص البالغين)، والفئة الخامسة بعمر يزيد عن 14 سنة (ضعف القوة المثلى لأقراص البالغين)، يتمتع بدقة إجمالية مقدارها 83.4% للأموديـاكوين و99.9% للأرتيسونات.

الاستنتاج: تعد الطريقة المقترحة لاستخدام المعطيات المرجعية للوزن بالنسبة للعمر المستمدَّة من البلدان التي تتوطنها الملاريا أداة مفيدة لتصميم جرعات النظم العلاجية المستندة على الوزن بالنسبة للعمر لتسجيل الأدوية المضادة للملاريا واستخدامها ميدانياً.

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