Tropical Medicine and International Health doi:10.1111/j.1365-3156.2006.01610.x

VOLUME 11 NO 5 PP 589–596 MAY 2006

Tolerability of amodiaquine and sulphadoxine-pyrimethamine, alone or in combination for the treatment of uncomplicated *Plasmodium falciparum* malaria in Rwandan adults

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Summary

OBJECTIVE To assess the tolerability and efficacy of amodiaquine (AQ) + sulphadoxine-pyrimethamine (SP), the first-line malaria treatment in Rwanda.

METHOD Randomized, double-blind trial in 2003 in Kigali town. A total of 351 adult patients with uncomplicated *Plasmodium falciparum* malaria were randomly allocated to one of the following treatments: AQ + SP, AQ or SP. We followed patients until day 14 after treatment and recorded adverse events (AEs) and clinical and parasitological outcomes.

RESULTS One hundred and eighteen patients reported at least one AE: 40% in the AQ, 39% in the AQ + SP and 21% in the SP groups. The AE was classified as possibly related to the antimalarial treatment for 86 patients. The Risk Ratio for at least one AE after treatment was significantly and about fourfold higher in patients receiving AQ or AQ + SP than in patients receiving SP. Pruritus and fatigue were significantly more frequent in patients treated with AQ or AQ + SP than in those receiving SP. Severe AEs, such as fatigue, nausea, dizziness and vomiting, were observed in four patients treated with AQ, in 10 treated with AQ + SP and in one patient treated with SP.

CONCLUSION Amodiaquine + SP is not well tolerated and a substantial proportion of patients experienced pruritus and fatigue, thus decreasing their compliance and compromising the first line treatment implementation at national level. This renders AQ-containing regimens sub-optimal; better-tolerated treatments should be identified.

keywords *Plasmodium falciparum* malaria, Rwanda, amodiaquine, sulphadoxine-pyrimethamine, tolerability

Introduction

Amodiaquine (AQ) is a 4-aminoquinoline similar to chloroquine (CQ) that has been widely used to treat and prevent malaria, as well as other diseases such as rheumatoid arthritis and lupus erythematosus. It was introduced as an alternative to CQ and at first appeared to be active against CQ-resistant *Plasmodium falciparum*. The drug was added to the WHO Model List of Essential Drugs in 1977, removed in 1979 because of its similarity to CQ and the need to choose the cheapest product available, and reinstated in 1983 with the recommendation of using it when CQ was ineffective or inappropriate. In the mid 1980s, fatal adverse drug reactions (an appreciable incidence of hepatitis and agranulocytosis) were reported in travellers on AQ prophylaxis (Hatton *et al.* 1986; Neftel *et al.* 1986). As a result, the manufacturer advised against the use of AQ for prophylaxis and in 1988 WHO removed it for a second time from the Essential Drugs List. In 1993 WHO stated that AQ could be used if the risk of infection outweighed the potential risk for adverse drug reactions. Following an extensive review (Olliaro *et al.* 1996), recommendations were modified to reinstate AQ as an option for treating falciparum malaria (WHO 1996). Recently, increasing attention has been given to therapies combining antimalarial drugs with different modes of action. Hence in 2002 the application for the inclusion of AQ was reviewed because of evidence of efficacy and cost-effectiveness, but this was deferred pending more detailed information on its safety (WHO 2002a). To respond to this request, WHO commissioned a Cochrane systematic review in which a total of 371 studies where AQ was used for malaria and other diseases were analysed (MacLehose *et al.* 2003). The review concluded that AQ treatment was

not associated with increased risk of white cell adverse events (AEs), liver toxicity or other severe AEs. In addition, comparative studies for which white blood cells (WBC) and neutrophil counts were available were analysed (WHO 2003a). The data showed that antimalarial drug treatment with AQ [alone or combined with sulphadoxine-pyrimethamine (SP) or artesunate (AS)], CQ and SP may be associated with a decline in the total white cell and neutrophil counts with a small proportion of patients developing neutropenia during follow-up. No significant differences were found between the different drugs thus supporting the conclusion that therapeutic use of AQ does not appear to be associated with an increased risk of neutropenia compared with the other commonly used antimalarial drugs.

In Rwanda the combination amodiaquine + sulphadoxine-pyrimethamine (AQ + SP) was implemented in 2001 as first-line treatment for uncomplicated *P. falciparum* malaria. Following its introduction, anecdotal but not well-documented reports from private practitioners of several cases of severe fatigue after treatment with AQ + SP reached the National Malaria Control Program in Kigali. A clinical trial aimed at documenting AEs after AQ + SP treatment was therefore carried out and the results are reported below.

Materials and methods

Study design, sites and patients treatment

This was a randomized, double-blind trial. The study was carried out in August–December 2003 in Kicukiro Health Centre, Kigali, Rwanda. The area is endemic for malaria and transmission is perennial with two rainy seasons in March–May and in October–December. Patients with suspected clinical malaria were screened and included in the study if they met the following criteria: age ≥15 years; *P. falciparum* mono-infection with parasite density between 1000 and 100 000/μl; fever (axillary temperature ≥37.5 °C) or history of fever in the preceding 48 h; packed cell volume (PCV) >15%. Patients with severe malaria or having any other disease, those with known allergy to the drugs to be used and women during the first trimester of pregnancy were excluded. The study was reviewed and approved by the Ministry of Health of Rwanda and by the Ethical Committee of the Institute of Tropical Medicine, Antwerp, Belgium.

Procedures

After signing the informed consent form, patients were assigned a sequential number corresponding to a sealed envelope containing one of the three study treatments: AQ + SP, AQ + placebo and SP + placebo. All treatments were identical in appearance as the placebo tablets mimicked either AQ or SP. The treatment envelopes were prepared in Belgium according to a number list in which the type of treatment was randomly allocated in blocks of 15. SP (500 mg sulphadoxine and 25 mg pyrimethamine base tablets; F. Hoffmann-La Roche Ltd) was given as a single dose on the first day (25 mg/kg based on sulphadoxine component) plus placebo given once a day for 3 days. AQ (200 mg base tablets; Parke-Davis) was dispensed once a day for 3 days (10 mg/kg/day) with placebo the first day for SP. The combination AQ + SP was given as follows: AQ + SP for the first day and AQ on the second and third day given once a day. Treatment was administered under direct observation. A full dose was re-administered if the patients vomited within 30 min after treatment. Patients were asked to return to the clinic 24 and 48 h later for drug administration and for scheduled tests at 72 h, and at days 7 and 14. If the patient did not report for scheduled visits every effort was taken by the nurses to locate him/her at his/her home address. Patients were encouraged to return to the health centre any time they felt unwell. A blood slide for parasitaemia was collected at day 0, 2 and 3 and at days 7 and 14. The follow-up was not extended until day 28 as the main objective of the study was to study AQ tolerability and not its efficacy. Thick blood films were stained with Giemsa. Parasite density was determined on the basis of the number of parasites per 200 WBC on a thick film, assuming a total WBC count of 8000/μl. If gametocytes were seen, the gametocyte count was extended to 1000 WBC. PCV (measured by microhaematocrit centrifugation), total and differential WBC counts and liver function tests, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were assessed at day 0 and 7. A full course of quinine was administered as rescue treatment in line with the Rwandan National Treatment Guidelines.

The primary endpoint of the study was treatment tolerability. All AEs were recorded on the Clinical Record Form and, if necessary, were immediately referred to the nearby university hospital. An AE was defined as 'any unfavourable and unintended sign, symptom, or disease temporally associated with the use of the drug administered'. A causality assessment of the AEs was done by the physician managing the patients on site and according to the guidelines of WHO-Uppsala Monitoring Centre (WHO-UMC). The definitions are as follows: Unlikely 'a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible

explanations'; Possible 'a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear'; Probable/likely 'a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal'; Certain 'A clinical event, including laboratory test abnormality occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary'. In the present study, given the complexity of defining a 'certain' AE, we used the first three definitions.

As a secondary outcome we measured the efficacy of the different treatments until day 14 according to the standard WHO (2002b, 2003b) classification: Early Treatment Failure (ETF) was defined as a patient developing: (i) danger signs of/or severe malaria on days 1, 2 or 3 with parasitaemia; (ii) parasite density at day 2 is greater than at day 0; (iii) axillary temperature ≥37.5 °C on day 3 with parasitaemia and (iv) parasite density at day 3 ≥25% of that at day 0. Late Clinical Failure (LCF) was defined as a patient developing between day 4 and day 14 danger signs of/or severe malaria and/or parasitaemia with axillary temperature ≥37.5°C, without having been previously classified as ETF. Late parasitological failure (LPF) was defined as a patient developing parasitaemia by day 14 with axillary temperature <37.5 °C, without previously meeting any of the criteria for ETF or LCF. An adequate clinical and parasitological response (ACPR) was defined as absence of parasitaemia by day 14 without previously meeting any of the criteria for ETF or LTF. The overall rate of treatment failure (total treatment failure) was considered as ETF + LCF + LPF.

Statistical analysis

Data were double entered and validated using EpiInfo 6.4b. Descriptive statistics were used to summarize baseline values and demography. Chi-squared analysis was used to compare the proportions of ACPR. The risk difference for failure was calculated with 95% confidence interval and a two-sided Fisher test. Analysis of variance (ANOVA) was used for normally distributed continuous data, and parasite densities were normalized by logarithmic transformation. The non-parametric Kruskal–Wallis test was used to analyse continuous data with a skewed distribution. All analyses were performed using STATA statistical analysis software package version 8 (2003; Stata Corp., College Station, TX, USA).

Results

Three hundred and fifty-one patients (117 for each treatment group) were recruited and randomized to one of the three study treatments. At enrolment treatment groups had similar demographic and clinical characteristics (Table 1). Six patients were lost during follow-up, one in the AQ, three in the AQSP and two in the SP group.

Safety and tolerability

Mean WBC count increased between days 0 and 7 in all three groups. However, the group receiving SP alone or in combination, had a significantly lower mean WBC count at day 7 ($P = 0.0031$) (Table 2). Neutropenia (neutrophils <1000/μl) was observed in a small proportion of patients at

Table 1 Baseline characteristics in the three groups of patients

	AQ ($n = 117$)	AQ + SP ($n = 117$)	SP ($n = 117$)
Demography			
Female/male	37/80	34/83	63/54
Mean age in years (SD)	25.1 (9.3)	24.8 (9.7)	25.6 (8.9)
Clinical characteristics			
Weight in kg (SD) (min–max)	57.01 (7.6) (34–77.2)	55.54 (7.7) (33–74.6)	55.78 (8.5) (32.8–91.4)
Mean temperature (°C) (SD)	37.4 (1.3)	37.5 (1.3)	37.3 (1.2)
Geometric mean asexual *P. falciparum*/μl (95%CI)	13 501 (10 844–16 810)	13 940 (11 130–17 459)	15 074 (12 385–18 348)
Gametocyte rate (%)	2 (1.7)	2 (1.7)	3 (2.6)
Splenomegaly (%)	2 (1.7)	0	2 (1.7)
Packed cell volume (SD)	40.2 (6.3)	40.2 (5.5)	38.6 (6.6)

Table 2 Median WBC/μl and differential count at days 0 and 7 by treatment group

	AQ		AQ + SP		SP	
	d0 ($n = 111$)	d7 ($n = 109$)	d0 ($n = 112$)	d7 ($n = 109$)	d0 ($n = 111$)	d7 ($n = 90$)
WBC	4300 (1200–19 400)	5400 (2700–24 000)	4150 (1080–15 400)	4500 (2150–23 700)	4400 (1700–9700)	4750 (2000–10 800)
Neutrophils	2546 (434–14 162)	2652 (896–12 240)	2497 (180–6952)	1855 (682–8532)	2585 (540–7954)	1750 (480–5400)
Lymphocytes	1296 (276–7050)	2132 (446–11 280)	1245 (194–7700)	2024 (323–12 324)	1240 (351–4272)	2233 (992–4428)

Values in parentheses are ranges.

day 0: AQ = 7.2% (8 of 111), AQ + SP = 7.1% (8 of 112), SP = 4.5% (5 of 111) ($P = 0.6$) and at day 7: AQ = 1.8% (2 of 109), AQ + SP = 8.3% (9 of 109), SP = 6.7% (6 of 90) ($P = 0.1$). Four of these patients had persistent neutropenia from day 0 (one patient in the AQ group, two patients in the AQ + SP and one in the SP group), and 13 of them developed neutropenia later without significant difference between groups (AQ = 1, AQ + SP = 7, SP = 5, $P = 0.1$).

At enrolment the mean PCV (%) was similar in the three treatment groups (Table 1). By day 7, the mean PCV was significantly lower in the group receiving SP alone (35.2) when compared with the AQ alone (38.3) and the AQ + SP (37.0) groups ($P = 0.0004$).

A decrease of the mean concentration of AST and ALT between day 0 and day 7 was observed in all groups, with no significant differences between them (data not shown). At day 0 the mean blood pressure (systolic and diastolic) was similar among the three groups of patients. However, it was significantly lower at days 2 and 3 for patients treated with AQ or AQ + SP, when compared with those treated with SP alone. Values normalized at day 7 when no significant difference among treatment groups was observed (data not shown).

At least one AE (with no causality assessment) was observed in 118 patients (35 of them had two or more), 47 of 117 (40.2%) in the AQ alone, 46 of 117 (39.3%) in the AQ + SP and 25 of 117 (21.4%) in the SP groups ($P < 0.003$). The most common AEs were: pruritus (34 patients), fatigue (27 patients), nausea (21 patients), vomiting (19 patients), dizziness (18 patients) and abdominal pain (13 patients) (Table 3). Overall, 159 AEs were recorded, 60% of them appeared after the administration of the treatment while the remaining ones were already present at enrolment and intensified after treatment.

Taking into account the causality assessment, 86 patients had an AE classified as possible or probable/likely related to drug treatment (Table 4). They were significantly more frequent in the AQ alone (33.3%, 39 of 117) and the AQ + SP (31.6%, 37 of 117) groups than in patients treated with SP alone (8.5%, 10 of 117) (Table 4); $RR_{AQ vs. SP} = 3.9$, 95% CI 2.2–6.9 ($P < 0.00001$); $RR_{AQ\,+\,SP vs. SP} = 3.7$, 95% CI 2.1–6.6 ($P < 0.00001$); $RR_{AQ vs. AQ+SP} = 1.05$, 95% CI 0.7–1.5 ($P = 0.89$). All cases of pruritus were classified as probably/likely caused by the treatment and they were significantly more frequent in patients treated with AQ alone (16.2%, 19 of 117) and AQ + SP (12.0%, 14 of 117) when compared with SP alone (0.9%, 1 of 117) ($P < 0.0001$). Pruritus usually started in the first 24 h after the first dose and lasted on average for 2.4 days (differences non-significant between groups). Similarly, cases of fatigue classified as related to the treatment were more frequently reported by patients in

Table 3 All adverse events (regardless of causality assessment) by treatment group (two or more adverse events in the same patient are considered separately) (%)

AE	AQ ($N = 117$)	AQ + SP ($N = 117$)	SP ($N = 117$)
Pruritus	19 (16.2)	14 (12.0)	1 (0.9)
Fatigue	8 (6.8)	13(11.0)	6 (5.1)
Nausea	7 (6.0)	7 (6.0)	7 (6.0)
Vomiting	3 (2.6)	9 (7.7)	7 (6.0)
Dizziness	8 (6.8)	7 (6.0)	3 (2.6)
Abdominal pain	5 (4.3)	4 (3.4)	4 (3.4)
Anorexia	1 (0.9)	3 (2.6)	1 (0.9)
Respiratory Infections	1 (0.9)	1 (0.9)	2 (1.7)
Cough	1 (0.9)	1 (0.9)	3 (2.6)
Diarrhoea	2 (1.7)	1 (0.9)	–
Headache	–	–	2 (1.7)
Dysphagia	–	1 (0.9)	1 (0.9)
Joint pain	1 (0.9)	1 (0.9)	–
Tinnitus	1 (0.9)	–	–
Extra pyramidal signs	1 (0.9)	–	–
Dysuria	–	–	1 (0.9)
Subicterus	1 (0.9)	–	–
Total	59 (50.4)	62 (53.0)	38 (32.5)

Table 4 Adverse event (AE) causality assessment by treatment group (%)

	Treatment	AQ ($n = 117$)	AQ + SP ($n = 117$)	SP ($n = 117$)	Total ($N = 351$)
All AEs		47 (39.8)	46 (39.0)	25 (21.2)	118 (33.6)
Unlikely	Non severe	8 (6.8)	8 (6.8)	14 (12.0)	30 (8.5)
	Severe	–	1 (0.9)	1 (0.9)	2 (0.6)
	Total unlikely	8 (6.8)	9 (7.7)	15 (12.8)	32 (9.1)
Possible	Non severe	6 (5.1)	9 (7.7)	5 (4.3)	20 (5.7)
	Severe	1 (0.9)	1 (0.9)	–	2 (0.6)
	Total possible	7 (6.0)	10 (8.5)	5 (4.3)	22 (6.3)
Probable/likely	Non severe	29 (24.8)	19 (16.2)	5 (4.3)	53 (15.1)
	Severe	3 (2.6)	8 (6.8)	–	11 (3.1)
	Total probable/likely	32 (27.3)	27 (23.1)	5 (4.3)	64 (18.2)
	Total possible/probable/likely	39 (33.3)	37 (31.6)	10 (8.5)	86 (24.5)

the AQ alone (6.8%, 8 of 117) and AQ + SP (11.1%, 13 of 117) groups when compared with the SP alone group (0.9%, 1 of 117) ($P < 0.005$). Ten of these patients (all of them having taken AQ: 3 AQ alone and 7 AQ + SP) had severe fatigue and six of them were hospitalized.

Overall, the AE was defined as severe in 15 patients (four in the AQ alone, 10 in the AQ + SP group and one in the SP alone) and nine were hospitalized (one in the AQ alone, seven in the AQ + SP group and one in the SP alone). Such severe AEs were fatigue, nausea, dizziness and vomiting. For two patients the relation between treatment and AEs was classified as unlikely; one treated with AQ + SP had an ETF with persistent vomiting and parasitaemia; the other treated with SP alone was still parasitaemic at day 3 with vomiting and fatigue. In the other seven hospitalized patients the relation between the treatment and the AEs was classified as probable/likely: one in the AQ alone and six in the AQ + SP groups. In six of them symptoms (fatigue, nausea, dizziness and vomiting) started between 24 and 72 h after treatment while in one patient they were already present at enrolment and worsened after treatment. All cases resolved within a week after hospitalization and were all defined as ACPR. No treatment interruption was required for any patient.

Clinical and parasitological efficacy

Early Treatment Failure was higher in the SP (18 of 115, 15.7%) than in the other two groups: 0.9% (1 of 116) in the AQ group and 0.9% (1 of 114) in the AQ + SP group. At day 14 no parasitological or clinical failures were observed in the AQ and AQ + SP groups, whereas 13 cases were observed in the SP alone group (10 parasitological and 3 clinical failures). The risk for failure (early and late) was similar between the AQ alone and the AQ + SP groups (RR = 0.98; 95% CI 0.06–15.5; $P > 0.9$), and more than 30-fold higher for the SP group when compared with the AQ alone (RR = 31.3; 95% CI 4.3–225.3; $P < 0.0001$) or with the AQ + SP groups (RR = 30.7; 95% CI 4.3–223.3; $P < 0.0001$).

Clearance of parasites was significantly faster for patients in the AQ and AQ + SP groups when compared with SP alone: (i) by day 2: 82.6% (95 of 115) and 88.8% (103 of 116) *vs.* 65.8% (75 of 114) ($P < 0.0001$); (ii) by day 3: 97.4% (112 of 115), 99.1% (114 of 115) *vs.* 70.9% (78 of 110) ($P < 0.0001$). Similarly, fever clearance was faster in the AQ and AQ + SP groups when compared with SP alone: (i) by day 2: 100% (115 of 115) and 99.1% (115 of 116) *vs.* 86.8% (99 of 114) ($P < 0.0001$); (ii) by day 3: 100% (115 of 115) and 100% (115 of 115) *vs.* 92.7% (102 of 110) ($P < 0.0001$). Few patients had gametocytes at recruitment (Table 1). Among those without gametocytes at day 0, gametocyte carriage was significantly higher in the group receiving SP alone when compared with the other two treatments. At day 7: SP alone 22.3% (21 of 94); AQ + SP 0.9% (1 of 111), AQ alone 3.5% (4 of 114) ($P < 0.0001$); and at day 14: SP alone 20.4% (19 of 93); AQSP 0.9% (1 of 111), AQ alone 0.9% (1 of 113) ($P < 0.0001$).

Discussion

Amodiaquine + SP and AQ alone had similar efficacy and were significantly better than SP alone; a significantly faster parasite and fever clearance was also observed. This can be attributed to both the anti-inflammatory/antipyretic properties of AQ and to the lower SP efficacy. True failure is likely to be much higher as the follow-up was only until day 14 after treatment. However, the main objective of this trial was to describe and quantify patient's tolerability to AQ and this is the main reason why follow-up was not extended further. In Rwanda, combining AQ with SP does not seem to have any advantage over AQ monotherapy, confirming previous data collected from the same area

(Rwagacondo *et al.* 2003). This is in contrast with reports from other countries in which AQ + SP had a significantly higher efficacy than AQ alone (Basco *et al.* 2002). However, most studies have been carried out in children rather than adults. Considering that the risk of treatment failure can change with age, results between studies investigating different age groups are hardly comparable.

Though treatment containing AQ, either alone or combined with SP had higher efficacy than SP alone, it was associated with a fourfold higher risk of AE, the most frequent being pruritus and fatigue. These results validate the anecdotal reports, mainly from Rwandan practitioners of severe fatigue in patients treated with AQ + SP. In most recent trials fatigue following administration of AQ with or without SP has been rarely reported (Basco *et al.* 2002), possibly because they have been carried out in children where transient fatigue might be difficult to recognize (Oduro *et al.* 2005; Yeka *et al.* 2005). Fatigue can be explained by transient toxic myopathy and/or neuropathy, already described in association with AQ or CQ use, which normally is followed by complete recovery on discontinuation of the drug (Estes *et al.* 1987). Generalized pruritus, usually resolving in a short time, is a common side effect in African patients treated with CQ or AQ. The mechanism is still uncertain but similar results were reported from Uganda and Cameroon where a higher frequency of pruritus was observed in patients treated with AQ than in those treated with SP, though the difference was not statistically significant (Staedke *et al.* 2001).

In the mid-1980s, serious and life threatening reactions were reported in adult travellers under AQ chemoprophylaxis (Hatton *et al.* 1986; Neftel *et al.* 1986), agranulocytosis, neutropenia and hepatitis being the most common conditions mentioned in the case reports. The mechanism of AQ-induced agranulocytosis remains unclear, but both direct cytotoxicity and immune-mediated mechanisms have been implicated (Maggs *et al.* 1988; Clark *et al.* 1990; Harrison *et al.* 1992). No serious AEs related to WBC were observed in our series of patients. Some of them developed neutropenia during the first week of follow-up, but differences among treatment groups were not significant. Patients treated with SP alone had lower mean WBC count at day 7, which is probably due to the low treatment efficacy. No hepatotoxicity was observed. When used prophylactically the risk of WBC dyscrasia has been estimated in one of 2200 users with a fatality rate of one of 31 300 while that of serious hepatic disorder was estimated in one of 15 650. The overall fatality rate was estimated at 1/15 650 (Phillips-Howard & West 1990). When AQ is administered as treatment, severe AEs seem to be rare (MacLehose *et al.* 2003; Olliaro & Mussano 2003), although the question on the potential toxicity of repeated treatments, likely to be common in malaria-endemic areas, remains open. Our sample size was not large enough to detect possible severe AE such as agranulocytosis, neutropenia and hepatitis. Nevertheless, a significantly higher frequency of mild and severe AEs was observed in patients treated with either AQ alone or AQ + SP with no significant difference between these two groups, indicating that AQ itself, regardless of the co-administered drug is not well tolerated. In 2001, AQ + SP was introduced in Rwanda as first-line treatment for uncomplicated falciparum malaria to rapidly replace CQ that had become ineffective, with clinical failure (early and late) in the years 1999–2000 ranging from 16.7% to 56.1% (http://www.eanmat.org). However AQ + SP has always been considered an interim strategy to be replaced with a more efficacious treatment, possibly an artemisinin-based combination. In 2002 AQ + SP gave significantly better results than SP combined with AS (Rwagacondo *et al.* 2003) and in 2003, AQ + AS was tested against AQ alone with good results, but higher AQ resistance was observed compared to the previous year (Rwagacondo *et al.* 2004). More recent clinical trials carried out in Rwandan children in the years 2003 and 2004 have showed a 28-day cure rate of 74% and 64% respectively. In those trials, the two artemisinin-based combination treatments tested (artemether-lumefantrine and dihydroartemisinin-piperaquine) had a significantly higher tolerability and efficacy than AQ + SP (Karema *et al.* in press).

The implementation of AQ + SP as first line treatment in Rwanda has been difficult because of the low tolerability anecdotally reported in adult patients. This was such a problem that several practitioners, mainly in Kigali, the capital city, refused to use it for their malaria patients. There have been reports of patients refusing to take the prescribed treatment because they were worried about the possible AEs, mainly about fatigue. Our findings confirm that AQ + SP is not well tolerated and a substantial proportion of patients experience pruritus and fatigue. Unfortunately, this compromises the antimalarial drug policy in Rwanda as practitioners might be less likely to prescribe the first line treatment or, when they do so, patients might be less likely to comply. Considering that AQ + SP has always been considered as an interim strategy and that AQ resistance is increasing (Rwagacondo *et al.* 2004), the Rwandan drug policy should be reviewed and alternative treatments should be identified as soon as possible.

Acknowledgements

We thank Prof. J. Plaizier-Vercammen at Farmaceutische Technologie & Fysische Farmacie Vrije Universiteit Brussel

for supplying the placebo tablets. We thank Jill and Chris Curtis for helpful comments on the manuscript. We are grateful to the patients as well as the staff at the sentinel sites for their contribution to this study. CF is funded by the Sir Halley Stewart Trust. The study was financed by the Belgian Development Cooperation (DGIS) in collaboration with the Prince Leopold Institute of Tropical Medicine, Antwerp.

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Tolérance de l'amodiaquine et de la sulfadoxine-pyrimethamine administrés individuellement ou en combinaison pour le traitement de la malaria à *Plasmodium falciparum* non compliquée au Rwanda

OBJECTIF Mesurer la tolérance et l'efficacité de l'amodiaquine (AQ) + la sulfadoxine-pyrimethamine (SP), le traitement de première ligne au Rwanda.
MÉTHODE Une étude randomisée en double aveugle conduite en 2003 dans la ville de Kigali. 351 patients adultes avec une malaria non compliquée à *P. falciparum* ont été repartis à l'un des traitements suivants: AQ + SP, AQ ou SP. Nous avons suivi ces patients jusqu'au jour 14 après le traitement et avons enregistré les effets adverses, les résultats cliniques et parasitologiques.
RÉSULTATS 118 patients ont rapporté au moins un effet adverse: 40% dans le groupe AQ, 39% dans le groupe AQ + SP et 21% dans le groupe SP. Les effets adverses étaient la cause possible des médicaments chez 86 patients. Le risque ratio pour au moins un effet adverse suite au traitement était significativement et environ 4 fois plus élevé chez les patients du groupe AQ ou AQ + SP que chez les patients du groupe SP. Un prurit et de la fatigue étaient significativement plus fréquents chez les patients traités avec AQ ou AQ + SP que chez ceux traits avec SP. Des effets adverses sévères tels que fatigue, nausée, malaises et vomissements ont été observés chez 4 patients traités avec AQ, 10 patients traités avec AQ + SP et 1 patient traité avec SP.
CONCLUSION AQ + SP n'est pas bien toléré et une proportion substantielle de patients ont présenté un prurit et de la fatigue, réduisant par conséquent leur compliance et compromettant l'implémentation de ce traitement combiné au niveau national. Cela rend les régimes contenant de l'AQ peu optimaux. Des traitements mieux tolérés devraient être identifiés.

mots clés *Plasmodium falciparum* malaria, Rwanda, amodiaquine, sulfadoxine-pyrimethamine, tolérance

Tolerabilidad frente a la amodiaquina y la sulfadoxina pirimetamina, solas o en combinación, para el tratamiento de malaria no complicada por *Plasmodium falciparum* en adultos de Ruanda

OBJETIVO Valorar la tolerabilidad y la eficacia de la amodiaquina + sulfadoxina pirimetamina, la primera línea de tratamiento para la malaria en Ruanda.
MÉTODO Ensayo aleatorizado, doble ciego, realizado en el 2003 en la población de Kigali. Se asignó aleatoriamente uno de los siguientes tratamientos a 351 pacientes adultos con malaria no complicada: AQ + SP, AQ o SP. Se siguieron los pacientes hasta el día 14, después del tratamiento, registrando los eventos adversos y los resultados clínicos y parasitológicos.
RESULTADOS 118 pacientes reportaron al menos un evento adverso: 40% en el grupo AQ, 39% en el de AQ + SP y 21% para SP. El evento adverso fue clasificado como posiblemente relacionado con el tratamiento antimalárico en 86 pacientes. El riesgo relativo para al menos un evento adverso después del tratamiento fue significativo y alrededor de cuatro veces mayor en pacientes recibiendo AQ o AQ + SP que en pacientes recibiendo SP. El prurito y el cansancio fueron significativamente más frecuentes en pacientes AQ o AQ + SP. Se observaron eventos adversos severos, como fatiga, nausea, mareo y vómitos en cuatro pacientes tratados con AQ, en 10 tratados con AQ + SP y en uno que recibió SP.
CONCLUSIÓN La AQ + SP no es bien tolerada, y una proporción sustancial de pacientes experimentaron prurito y cansancio, disminuyendo por lo tanto el cumplimiento y comprometiendo la implementación de la primera línea de tratamiento a nivel nacional. Esto hace que los regimenes que contienen AQ no sean óptimos. Se deberían identificar tratamientos que fuesen mejor tolerados.

palabras clave malaria, *Plasmodium falciparum*, Ruanda, amodiaquina, sulphadoxina-pirimetamina, tolerabilidad