

Adherence to the combination of sulphadoxine–pyrimethamine and artesunate in the Maheba refugee settlement, Zambia

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Summary

Artemisinin-based combination therapy (ACT) is one strategy recommended to increase cure rates in malaria and to contain resistance to *Plasmodium falciparum*. In the Maheba refugee settlement, children aged 5 years or younger with a confirmed diagnosis of uncomplicated falciparum malaria are treated with the combination of sulphadoxine–pyrimethamine (1 day) and artesunate (3 days). To measure treatment adherence, home visits were carried out the day after the last treatment dose. Patients who had any treatment dose left were considered certainly non-adherent. Other patients' classification was based on the answers to the questionnaire: patients whose caretakers stated the child had received the treatment regimen exactly as prescribed were considered probably adherent; all other patients were considered probably non-adherent. Reasons for non-adherence were assessed. We found 21.2% (95% CI [15.0–28.4]) of the patients to be certainly non-adherent, 39.4% (95% CI [31.6–47.6]) probably non-adherent, and 39.4% (95% CI [31.6–47.6]) probably adherent. Insufficient explanation by the dispenser was identified as an important reason for non-adherence. When considering the use of ACT, the issue of patient adherence remains challenging. However, it should not be used as an argument against the introduction of ACT. For these treatment regimens to remain efficacious on a long-term basis, specific and locally adapted strategies need to be implemented to ensure completion of the treatment.

keywords malaria, adherence, sulphadoxine–pyrimethamine, artesunate, artemisinin-based combination therapy, Zambia

Introduction

Malaria causes between 300 and 500 million new infections and kills 1 to 2 million people per year, predominantly among young African children (Bloland 2001; WHO 2001). The number of effective anti-malarials available is in bleak contrast with the magnitude of the disease (Marsh 1998; White *et al.* 1999; Trape 2001). Chloroquine efficacy against *Plasmodium falciparum* is declining all through Africa, and the same is true for sulphadoxine–pyrimethamine (SP), although both drugs are still used as first-line treatment in most African settings (Trape 2001). The consequences are recrudescence of resistant parasite populations, increased mortality and morbidity and higher transmission rates with a greater risk for epidemics (Price & Nosten 2001; Trape 2001). One strategy that has been shown to increase cure rates and decrease the development of drug resistance is the introduction of artemisinin-based combination therapy (ACT) (White &

Olliaro 1996; White 1999). In Africa, the large-scale use of ACT as first-line treatment for uncomplicated malaria is recent and limited: at the time of this writing, artemether and lumefantrine is used in one province of South Africa, KwaZulu-Natal and in Zambia; amodiaquine and artesunate is used in Zanzibar and Burundi (Baker & Barnes 2001; Roll Back Malaria 2003).

For the broader use of ACT in the continent to be successful, several issues need to be addressed (Bloland *et al.* 2000). One is related to patient's treatment adherence (compliance) – the degree to which a patient adheres to the treatment schedule prescribed – which is determined by numerous and intertwining factors, such as perception of disease, acceptance of the treatment, its cost, the complexity of the schedule, the quality of prescription, or the patient's clinical improvement. The consequences of poor patient adherence are serious: cure rates for patients who do not complete their treatment are likely to be lower, and exposure to too low a drug level risks the development

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of resistance (Berkow 1992; White & Olliaro 1996). To our knowledge, adherence to ACT has only been studied in South-East Asia (Na-Bangchang *et al.* 1997; Shwe *et al.* 1998).

At the time of our study, the Zambian government was considering changing the national policy which prescribed chloroquine as first-line, and SP as second-line treatment, to the introduction of ACT. The Central Board of Health authorized Médecins Sans Frontières (MSF) to use the combination of SP and artesunate (SP/AS) in the Maheba refugee settlement for the treatment of up to age 5 years. We studied patient adherence to this combination and assessed reasons for non-adherence.

Materials and methods

Study area and population

Our study took place in the Maheba refugee settlement, which has existed since 1971 and is situated in the North-Western Province of Zambia. Most of the estimated 54 000 refugees come from Angola; others are from Democratic Republic of Congo, Rwanda and Burundi (UNHCR 2002). Maheba is divided into eight zones, A to H. Zone H, where our study took place, has a target population of about 15 000 refugees, who mainly arrived after the last upsurge of the Angolan war in 1998. Malaria is considered Zambia's highest cause of morbidity and second highest cause of mortality in children under 5. Prevalence of resistance of 54% and 26% have been measured for chloroquine and SP, respectively (NMCC 1999; Bijl *et al.* 2000). In the health clinic of zone H in Maheba (clinic H, supported by MSF), in the first trimester of 2002, 35.8% of the outpatient consultations were due to malaria (unpublished data). In this clinic, since November 2001, all children aged 5 years and younger, with a history of fever and for whom the diagnosis of uncomplicated falciparum malaria is confirmed by a rapid HRP2 test (Paracheck[®]), are prescribed a unique dose of SP (25 mg sulphadoxine/kg) on day 0, and 3 days of AS (4 mg/kg/day) starting on day 0. The drugs are provided free of charge. The clinic's pharmacist dispenses the prescribed treatment loosely in medication sachets and explains how it should be taken. The dose of SP, as well as the first dose of AS, are supposed to be taken under supervision at the clinic.

Study objective

The objective of the study was to measure patient adherence to ACT in children up to age 5 years under routine conditions of prescription in a refugee settlement. In order to limit bias as much as possible, a minimum of

interventions was undertaken. Our knowledge of the routine practices in the health centre, the base for the assessment tools, was founded on an informal account of the health staff. In order not to influence these practices, we did not look to systematically verify them beforehand.

Design and procedures

During the study period, all children aged 5 years or younger, who were reported to have received SP/AS during outpatient consultation hours, were included in the study and visited at home the day after the last treatment dose (day 3). Axillary temperature on day 0 and concomitant treatment prescribed were copied beforehand from the clinic's register. In case a child belonged to a household already visited, the child was excluded from the study, so that no family was interviewed twice. Apart from the study team, no one was aware of this visit. At the beginning of the visit, written informed consent from the patient's caretaker was obtained. The patient's axillary temperature was taken. A structured questionnaire, translated into the three languages most frequently used in the clinic's catchment area and field-tested, was applied to the caretakers. The questionnaire assessed the intake of AS by the child, both through spontaneous account and a systematic review of the intake of every single dose. Under the assumption that, according to the treatment protocol, the dose of SP was systematically taken at the clinic, questions did not refer to the intake of SP. Socio-demographic information on the patient was collected and the caretaker's language, age and education level, the number of people who spent the night at the house, as well as, for women, the number of children cared for, were investigated. The questionnaire was completed by counting any remaining tablets, both of AS and SP. In case tablets remained, the caretaker was asked to specify why not all tablets were given to the child. The team of interviewers was closely supervised by the study coordinator.

Definition of adherence

Children whose caretakers showed a medication sachet still containing AS at the moment of the home visit, were considered as certainly non-adherent. In case the patient could not show any medication sachet, or in case the medication sachet was empty, the answers to the questionnaire were used to classify the patients: those patients whose caretaker stated to have given the AS, exactly following the treatment protocol, were considered probably adherent; patients were considered probably non-adherent if, according to the caretaker, the patient took the AS in any other way than prescribed.

Sample size

Without any reference of data related to adherence to the combination of SP/AS, we assumed a non-adherence of 20%. With a precision of 7%, an α -error of 5%, and after accounting for 20% loss to follow-up or withdrawal, 149 patients were required.

Pharmacist observations and interviews of caretakers at the end of the consultation

In order to identify possible factors influencing adherence, two additional investigations were carried out. For 1 week after the adherence assessment, the pharmacist was systematically observed while explaining the SP/AS prescription to the guardians of children of 5 years or below; these guardians were different from those previously interviewed. A check-list was used to verify what information, needed to take the treatment correctly, was given: timing of drug intake, importance of completing the treatment, asking the caretaker if he or she understood the explanation, observation of the supervised treatment dose. As the observers stood next to the patient during the explanation, the pharmacist knew a study was being conducted, but he was blinded to the purpose of the observation.

During that same week, patient's caretakers were systematically interviewed after leaving the pharmacy and right before leaving the clinic, in order to assess their understanding of the SP/AS prescription. A short questionnaire, asking for a spontaneous account on how the treatment was to be given to the child, followed by a systematic questioning for each treatment dose, was completed.

Statistical analysis

Data of the adherence assessment, the pharmacist observations and the caretaker interviews were double-entered separately in three different databases and analysed using Epi Info 6.04dfr (CDC, WHO). Sample characteristics and patient's classification were described as proportions and presented with 95% confidence intervals (CI). The association between non-adherence and potential risk factors was investigated, using first certain non-adherence as such, and second certain and probable non-adherence combined as the outcome; the association was measured through relative risk (RR) estimates with the 95% CI.

Ethical approval

The study protocol was approved by the Zambian Research Ethics Committee.

Results

Between 7 and 28 February 2002, 162 children were treated with the combination SP/AS and thus included in the study. The median age was 12 months (range: 1–71) and mean axillary temperature on the day of consultation was 37.8 °C (SD: 1.2) (Table 1). On day 3, the home of 18 patients (11.1%) could not be found. These children were considered lost to follow-up. Two patients (1.2%) who had not received the study treatment because of temporary drug shortage were withdrawn from the study. Consequently, a total of 142 (87.7%) home visits were held for further analysis. The majority (95.1%) of the patient's caretakers were women and the median age of all caretakers was 28 years (range: 16–49). A median number of four people stayed at the house the night before the visit (range: 2–11). The median number of children taken care of by women the day before the visit was 3 (range: 1–9). More than half of the caretakers (55.6%) had never attended school at all.

For 110 patients (77.5%) the medication sachet was shown to the home visitors. Thirty patients (21.2%) were considered certainly non-adherent, 28 of whom had AS left in the sachet and two had both AS and SP. For 20 patients (66.7%) one AS treatment dose remained, for eight patients (26.7%) two AS doses, and for two patients (6.6%) three AS doses remained. For these patients with tablets remaining, 10 caretakers stated to have forgotten, three to have kept the tablets for the future, one that the

Table 1 Socio-demographic and clinical characteristics of patients on inclusion

	Number	Percentage
Nationality (<i>n</i> = 161)		
Angolan	154	95.7
Others	7	4.3
Language (<i>n</i> = 162)		
Lunda/Luvale	109	67.3
Umbundu	36	22.2
Others	17	10.5
Gender (<i>n</i> = 162)		
Male	83	51.2
Female	79	48.8
Age (<i>n</i> = 162)		
<2 years	104	64.2
2 years or more	58	35.8
Concomitant treatment (<i>n</i> = 161)		
Antipyretic only	136	84.5
Others	25	15.5
Temperature on inclusion (°C) (<i>n</i> = 155)		
<37.5	59	38.1
≥37.5 and <39.5	81	52.2
≥39.5	15	9.7

Table 2 Proportion of certain and probable (non-)adherence ($n = 142$)

	Number	Percentage	95% CI
Certainly non-adherent	30	21.2	[15.0–28.4]
Probably non-adherent	56	39.4	[31.6–47.6]
Probably adherent	56	39.4	[31.6–47.6]
Total	142	100.0	

child was cured and one that the child did not like the tablets; seven caretakers did not answer and eight gave still another reason. A further 56 patients (39.4%) were probably non-adherent, 46 (82.1%) of whom had taken all three doses but spread over the first 2 days. The remaining 56 patients (39.4%) were considered probably adherent. (Table 2) Children whose caretakers had received some education had a significantly lower risk to be non-adherent, both for certain non-adherence as the outcome (RR = 0.46, 95% CI [0.22–0.95]), and for certain and probable non-adherence combined (RR = 0.67, 95% CI [0.50–0.90]). For the latter, the caretakers having the same mother tongue as the pharmacist had a lower risk to be non-adherent (RR = 0.46, 95% CI [0.28–0.77]). None of the other risk factors assessed were found to be significantly associated with non-adherence.

During one week (27 February to 5 March 2002), 65 explanations by the clinic's pharmacist were observed. On average, the time spent on each explanation was <1 min. The pharmacist specified the moment when to take the three AS doses for all patients. For 64.6% ($n = 42$), he asked the caretaker whether or not he or she had understood his explanation. All patients were given the first dose of AS, together with the SP, to be taken at the health clinic. However, the pharmacist observed the intake of the drugs in only 16 cases (24.6%).

During the same period, 74 interviews of caretakers at the end of the consultation were conducted; for 54 (73.0%) the pharmacist's explanations had been observed just before. At the moment of the interview, 13.7% ($n = 10$) of the patients had not taken SP, and 19.2% ($n = 14$) had not taken the first dose of AS. Moreover, 39.7% ($n = 29$) of the caretakers could not state the correct day for each dose to be given at home. Finally, 10 caretakers (13.7%) stated they would not give the tablets to the child if the child would not appear sick anymore.

Discussion

In our setting, certain non-adherence to the combination SP/AS was 21.2%: there is no doubt that one of five patients did not complete the treatment within the set

timeframe of 3 days. Taking into consideration the verbal account of the caretaker, another 39.4% were classified as probably non-adherent. Therefore, non-adherence could be as high as 60.6% if the certain and probable results are combined. Weaknesses at the prescription level have been revealed, showing that an adequate fulfilment of this task should not be taken for granted. The pharmacist did not explain sufficiently the treatment schedule and did not check the intake of the first medication dose at the clinic. The caretaker had not always understood the treatment guidelines, a factor that might also be influenced by his or her education level or by different mother tongues. As two different samples were used (in order not to introduce bias), no conclusions can be drawn with regard to the poor explanations being the cause of poor adherence in Maheba. However, the results of both independent assessments show that the weaknesses at the prescription level might have played a role in patient adherence. However, the small sample size of the pharmacist observations and the caretaker interviews should caution against definitive interpretations of these outcomes.

To interpret our results, we looked at studies in Africa measuring adherence to chloroquine; however, few studies are available and the lack of a uniform methodology makes true comparison difficult. We found patient non-adherence in Maheba was rather high, which might be explained by several factors. First, a very strict definition was used, which influences the interpretation of our results: in spite of having ingested all tablets prescribed, patients were classified probably non-adherent if the day of intake was incorrect (different from one dose of AS per day). This contrasts with the other studies which consider only the quantity taken, and therefore, in comparison with our study, underestimate non-adherence (Ejezie *et al.* 1990; Yeneneh *et al.* 1993; Vundule & Mharakurwa 1996; Okonkwo *et al.* 2001; Nshakira *et al.* 2002). Secondly, in the other studies, better adherence was found in the intervention groups, among patients receiving pre-packaged drugs, or additional and targeted explanations. When measuring adherence, these interventions are likely to account for additional bias as people are automatically aware of a study taking place. In our study, we tried to measure treatment adherence while limiting similar bias as much as possible; no intervention methods were introduced and people only knew about the study once the treatment was supposed to be finished. Thirdly, living conditions in zone H of the Maheba refugee settlement are precarious. People represent very different backgrounds, knowledge and behaviour. While fleeing from violence and war, they functioned on survival mode often for many years, and did not have regular access to health care or education. Finally, although this aspect was not studied in particular, the

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presentation of the drugs loosely in sachets without clear marks of timing or dosage of the drugs, might also play a role in patient non-adherence. All these factors might explain the fact that non-adherence in Maheba was higher than expected.

However, looking at the results of the previously cited studies, non-adherence to chloroquine tablets and/or syrup varied between 9% and 79% (Ansah *et al.* 2001; Okonkwo *et al.* 2001; Yeboah-Antwi *et al.* 2001; Agyepong *et al.* 2002; Nshakira *et al.* 2002). For still other studies, where adherence has been assessed as part of Knowledge, Attitudes and Practices (KAP) or household surveys, non-adherence ranged from 6.3% to 83% (Deming *et al.* 1989; Ejezie *et al.* 1990; Yeneneh *et al.* 1993; Slutsker *et al.* 1994; Vundule & Mharakurwa 1996). In conclusion, whatever the method used, our results fall within the same range.

Implications of patient non-adherence with ACT lie both on individual and public health level. The incomplete elimination of the parasite exposes the patient to recurrent malaria attacks, increasing malaria-related morbidity and mortality. On the community level, it leads to development of parasite resistance, again augmenting malaria incidence, morbidity and mortality (Price & Nosten 2001). Methods to improve patient adherence comprise the use of instructive tools such as posters and videotapes, or the pre-packaging of tablets (Gomes *et al.* 1998). They have been shown to increase patient adherence, but are complex to implement and often produce limited results. The high turnover of patients in an African setting such as the Maheba refugee settlement limits the time spent with each patient. Increased investment of the health personnel, building a more constructive relation with the patients, taking the time to explain treatment schedules, and systematically making patients repeat the explanations, might be another solution. In any case, research on new, straightforward and field-adapted strategies is needed.

Conclusion

The use of ACT is one of the strategies in Africa to contain high resistance levels to anti-malarial drugs. Our study shows that its implementation should not be taken lightly and that certain difficulties, such as poor patient adherence, cannot be ignored. Poor adherence should not serve as an argument against the introduction of ACT, in the same way it was never drawn on to stop using chloroquine, in use for over 50 years. However, investment to improve patient adherence should be inherently related to initiating combination therapy. Once combination therapy is put well into place, adherence to the treatment should be monitored. The currently used but increasingly ineffective malaria drugs are likely to be replaced by more complex

treatment schedules. If we want to give a chance to the few alternatives available for the treatment of malaria, and ensure treatment efficacy for the coming years, the improvement of adherence is essential and needs to be addressed – as from today.

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