THERAPEUTIC EFFICACY OF SULFADOXINE-PYRIMETHAMINE IN UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA 3 YEARS AFTER INTRODUCTION IN MPUMALANGA

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Objectives. To assess therapeutic efficacy of sulfadoxine-pyrimethamine (SP) in treatment of uncomplicated *Plasmodium falciparum* malaria 3 years after introduction in Mpumalanga, South Africa.

Setting. Tonga district with a population of 116 418 and subject to seasonal malaria, with an average annual incidence of 3 200 cases.

Subjects. One hundred and nineteen malaria patients presenting to a sentinel surveillance clinic and recruited according to World Health Organisation (WHO) criteria.

Methodology. Patients satisfying WHO inclusion criteria were treated with a single oral dose of SP and the response of infection to treatment in each patient was routinely monitored clinically and parasitologically on days 1, 2, 3, 7, 14, 21, 28 and 42 post-treatment. One hundred and ten patients completed follow-up to day 42 or evidence of clinical or parasitological failure.

Results. The cure rate at day 42 was 93.6% (103/110). Two patients (1.8%, RII) were early treatment failures on day 3, while recrudescence (4.5%, RI) occurred in 5 patients on day 28 ($N = 3$) and on day 42 ($N = 2$).

Conclusion. In Mpumalanga *P. falciparum* remains sensitive to SP, with no significant difference between the baseline cure rate (94.5%) and the cure rate in the present study (93.6%).

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Chloroquine-resistant *Plasmodium falciparum* was first reported in East Africa in 1979 and has since spread throughout the continent.[1,2] Initial evidence of resistance from South Africa was noted during the early 1980s.[3-6] Routine programme monitoring and *in vitro* studies indicated the presence of *P. falciparum* chloroquine resistance in Mpumalanga, South Africa, from the mid-1990s, and between February and May 1997 a formal *in vivo* chloroquine resistance study was conducted in the province.[7,8] This investigation confirmed a high level (48.4% RI+RII+RIII of chloroquine resistance in *P. falciparum* parasites (Freese *et al.* — unpublished data). As a result, chloroquine was replaced with sulfadoxine/pyrimethamine (SP) as the first-line treatment of uncomplicated *P. falciparum* malaria in Mpumalanga in 1997. Assessment of SP effectiveness as primary treatment for uncomplicated *P. falciparum* malaria at introduction in the province revealed a 94.5% cure rate, and a combined RI and RII resistance of only 5.5%.[9] The current study was conducted to assess SP effectiveness as primary treatment for uncomplicated *P. falciparum* malaria 3 years after its introduction, as part of a routine programme and to monitor the local evolution of SP resistance.

METHODS AND MATERIALS

Patients

The study was conducted in Tonga health district, Mpumalanga, between January and May 2000, inclusive. All patients with clinical episodes compatible with malaria presenting at the two 24-hour primary health care clinics in the district, Mangweni and Naas, were tested for *P. falciparum* infection using an immunochromatographic card test (ICT Malaria P.f.).[10] Positive patients were then recruited according to established criteria, with inclusion criteria being age above 2 years, symptomatic uncomplicated *P. falciparum* mono-infection, *P. falciparum* asexual hyperparasitaemia above 1 000 parasites/µl blood, easy access to the patient's home, fully informed consent by patient or accompanying relatives in the case of minors, and axillary temperature above 37.5°C. Exclusion criteria included severe malaria, concomitant disease, mixed infection, intolerance of oral therapy, refusal to provide consent, and pregnancy. Criteria for withdrawal included patient choice, clinical deterioration necessitating hospital referral, patient non-compliance, loss to follow-up and protocol violation, including self-administration of other antimalarial drugs during follow-up.[11] Baseline information including age, gender, weight and place of residence was obtained from all study subjects.

Treatment

Patients were treated according to the guidelines of the Mpumalanga Department of Health, with a single oral dose of SP, corresponding to 25 mg/kg of sulfadoxine and 1.25 mg/kg

of pyrimethamine. After drug administration patients were observed for 1 hour to detect vomiting. If vomiting occurred within 30 minutes of drug administration a full dose was repeated. If vomiting occurred between 30 and 60 minutes post administration, an additional half dose was administered. No additional treatment was administered if vomiting occurred after 60 minutes. Patients with clinical treatment failure were referred to hospital for therapy with quinine.

Laboratory assessment and outcome measures

Clinical and parasitological assessment was conducted routinely on days 1, 2, 3, 7, 14, 21, 28 and 42 post-treatment. At each follow-up visit a thick blood smear was taken, body temperature was recorded and an assessment for adverse events was completed. Fever was defined as an axillary temperature exceeding 37.5°C. Parasitaemia was measured by counting the number of parasites against 300 leucocytes on a Giemsa-stained, finger-prick thick-blood film and multiplying the figure by 25, assuming a standard leucocyte count of 7 500/µl blood.

Parasitological success was defined as conversion from a positive smear at recruitment to a negative smear by day 7 and remaining negative until the end of the 42-day follow-up period. Parasitological treatment failure was defined as the presence of asexual *P. falciparum* parasites in the blood film between days 7 and 42 post-treatment. Parasite clearance time was the number of days from recruitment to the first smear with no asexual parasites. Fever duration was the number of days from recruitment to the day when axillary temperature was recorded as 37.5°C or below without a subsequent recorded increase in temperature. Recrudescence was defined as a negative blood film before day 7 and reappearance of parasites during the remaining follow-up period. Early treatment failure was defined as axillary temperature ≥ 37.5°C on day 2 and parasitaemia ≥ 25% on day 0, or axillary temperature ≥ 37.5°C on day 3 and any parasitaemia.[11] RIII was defined as a parasitaemia that remained above 25% of the initial count by day 2 and that continued to be positive on day 7.

Ethical consideration

Approval for the study protocol was obtained from the Mpumalanga Department of Health Ethical Committee. Fully informed consent was obtained before enrolment from each patient, or accompanying relatives in the case of minors.

Results

Baseline information

Between January and May 2000, 119 patients were recruited (Table I). Follow-up was completed for 108 patients (90.8%, 108/119) to days 7, 14 and 21; for 105 patients (88.2%) to day 28; and for 103 patients (86.6%) to day 42. One hundred and ten patients (92.4%, 110/119) completed follow-up to day 42 o until parasitological or clinical evidence of treatment failure. C the 9 patients who did not complete the study, 4 were lost to follow-up, 2 took other antimalarial drugs during follow-up, were referred to hospital because of persistent clinical symptoms, and 1 moved from the study area (Table II). The subjects lost to follow-up were as a result of inaccessibility aft severe flooding in the area.

Table I. Admission variables of patients with *P. falciparum* malaria

Number of patients	119
Males (%)	59 (49.6)
Females (%)	60 (50.4)
Age composition (%)	
< 10 years	29 (24.4)
10 - 20 years	44 (37.0)
21 - 30 years	19 (17.0)
31 + years	27 (22.7)
Mean age (yrs) (SD)	22.6 (± 17.2)
Age range (yrs)	2 - 79
Mean weight (kg) (SD)	46.5 (± 19.0)
Weight range (kg)	11.0 - 95.0
Mean initial temperature (°C) (SD)	40.0 (± 0.8)
Range on recruitment (°C)	37.6 - 41.0
Mean initial parasitaemia (parasites/µl)	29 886
Range on recruitment (parasites/µl)	1 563 - 332 000

Clinical and parasitological responses

There was a sharp decline in mean density of parasitaemia after SP treatment (Fig. 1). By day 2, fever had cleared in 47.8% of patients (54/113), while 79.1% (87/110) had cleared by day 3

Table II. Reasons for failure to complete study

	Days post-treatment								
Classification	D1	D2	D3	D7	D14	D21	D28	D42	Total
Withdrawal	0	0	2	0	0	0	0	0	2
Drop-outs	3	1	0	0	0	0	0	0	4
Movement	0	1	0	0	0	0	0	0	1
Referrals	0	2							2
Total	3	4	2	0	0	0	0	0	9

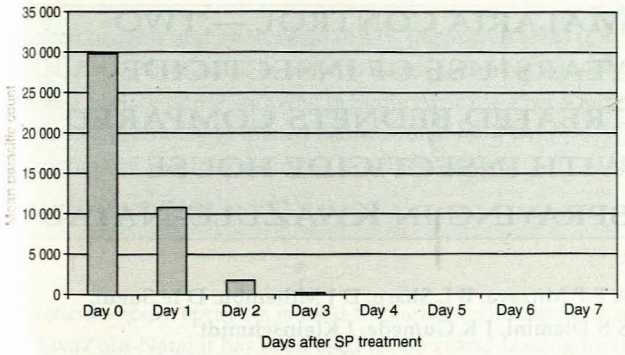

Fig. 1. Response of parasitaemia to sulphadoxine/pyrimethamine (SP) treatment.

and 95.5% (105/110) by day 7. By day 2, asexual parasites were absent in 49.6% of patients (56/113, while 84.6% (93/110) and 100% (108/108) were cleared of parasites by days 3 and 7 respectively. Of the 108 patients who were followed up until day 7, all (100.0%, S/RI) were cleared of asexual parasites. Of 110 patients who had complete follow-up until day 42 or until parasitological or clinical evidence of treatment failure, 103 (93.6%, 103/110) were radically cured, recrudescence occurred in 5 (4.6%, RI) on day 28 ($N = 3$) and day 42 ($N = 2$), and 2 cases (1.8%, RII) were early treatment failures on day 3 (Table III). Gametocytes were counted, peaking between days 7 and 28 (Fig. 2). No adverse events were reported by subjects during the study.

Table III. Classification of *in vivo* response to treatment (% (*N*))

Response	Patients
Parasitological and clinical success (S)	93.6 (103/110)
Recrudescence (RI)	4.6 (5/110)
Early treatment failure (RII)	1.8 (2/110)

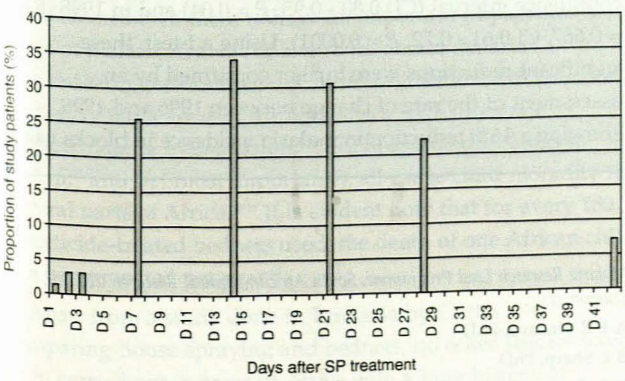

Fig. 2. Gametocyte rate after SP treatment.

Discussion

P. falciparum is still sensitive to SP in Mpumalanga, with a 93.6% cure rate, and a combined RI and RII resistance of only 6.4% after 3 years of general use. The baseline data at SP introduction demonstrated a sensitivity of *P. falciparum* to SP, with a cure rate of 94.5% and a combined RI and RII resistance of 5.5%.[9] An RIII response was not demonstrated in the previous study or in the current study. Although resistance of *P. falciparum* to SP of 52.0% was reported in KwaZulu-Natal after the drug had been in use for more than a decade (J Mthembu — unpublished data), little is currently known about the evolution rate of SP resistance, a shortcoming that is addressed by routine programme monitoring.

A disparity in fever and parasite clearance patterns, with symptoms persisting despite reduction in parasite load, was observed in the present study, confirming the findings of the previous study[9] and a report from The Gambia[12,13] in which patients treated with SP returned to clinics within the first few days after treatment with persistent symptoms. Slow reduction of clinical symptoms with SP treatment prompted 2 referrals, and may have resulted in 2 patients taking other antimalarial drugs during follow-up in the present study. In a Gambian study,[14] routine administration of paracetamol to control symptoms failed to prevent children treated with SP returning to the health service with symptoms. Combination therapy with antimalarial drugs may be necessary for cure and adequate symptom alleviation.

In the present study gametocytes peaked between days 7 and 28. This finding compares favourably with the previous study in Mpumalanga[9] and a Gambian study,[15] which found that 28.9% of patients treated with SP carried gametocytes at 2-week follow-up. SP has no known gametocytocidal properties and gametocyte generation and development appears to persist despite SP treatment.[16] A laboratory-based study in Mozambique[17] demonstrated that SP treatment may suppress gametocyte infectivity and possibly decrease *Anopheles arabiensis* infectivity after ingestion of viable gametocytes. The impact of increased gametocyte production on malaria transmission deserves further study.

A cure rate of 93.6% in patients treated with SP indicates that this drug remains effective for the treatment of acute uncomplicated *P. falciparum* malaria in Mpumalanga. The study gave no evidence of statistically significant differences between 1997 and 2000. The importance of protecting this relatively affordable therapy through combination with rapid-acting and preferably gametocytocidal antimalarial deserves urgent evaluation.

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