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 Plasmodium 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.12 Initial evidence of resistance from South Africa was noted during the early 1980s.24 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.27 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 — unpublished data).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%.28 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 Pf).39 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.13 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. 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 until parasitological or clinical evidence of treatment failure. Of the 9 patients who did not complete the study, 4 were lost to follow-up, 2 took other antimalarial drugs during follow-up, 2 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 after severe flooding in the area.

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

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%. 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 and a report from The Gambia 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, 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.

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.

The South East African Combination Antimalarial Therapy (SEACAT) evaluation, within which this study was nested, received financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and was jointly funded by the Mpumalanga Department of Health.
MALARIA CONTROL — TWO YEARS’ USE OF INSECTICIDE-TREATED BEDNETS COMPARED WITH INSECTICIDE HOUSE SPRAYING IN KWAZULU-NATAL

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Objectives. The objective of this study was to produce data indicating whether insecticide-treated bednets should replace insecticide house spraying as a malaria control method in South Africa. We report 2 years of preliminary data on malaria incidence comparing areas receiving insecticide-treated bednets and those subjected to house spraying in northern KwaZulu-Natal.

Design, setting and subjects. In order to measure significant reductions in malaria incidence between the two interventions, a geographical information system (GIS) was used to identify and create seven pairs of geographical blocks (areas) in the malaria high-risk areas of Ndumu and Makanis, Kwazulu-Natal. Individual blocks were then randomly allocated to either insecticide-treated bednets or house spraying with deltamethrin. Malaria cases were either routinely recorded by surveillance agents at home or were reported to the nearest health facility.

Results and conclusions. The results show that 2 years’ use of insecticide-treated bednets by communities in Ndumu and Makanis, Kwazu-Natal, significantly reduced the malaria incidence both in 1997 (rate ratio (RR) = 0.879, 95% confidence interval (CI) 0.80 - 0.95, P = 0.04) and in 1998 (RR = 0.667, CI 0.61 - 0.72, P = 0.0001). Using a t-test, these significant reductions were further confirmed by an assessment of the rate of change between 1996 and 1998, showing a 16% reduction in malaria incidence in blocks using insecticide-treated bednets.