EFFECTIVENESS OF SHORT-COURSE QUININE AND SINGLE-DOSE SULFADOXINE-PYRIMETHAMINE IN THE TREATMENT OF *PLASMODIUM FALCIPARUM* MALARIA IN MPUMALANGA PROVINCE, SOUTH AFRICA

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Introduction. Quinine therapy for 7 days remains the mainstay for treating hospitalised malaria cases in South Africa. However, limited resources, including available beds and staff, often result in early discharge of non-severe cases, with quinine tablets for outpatient use. The effectiveness of shorter course quinine therapy coupled with a long-acting antimalarial drug has never been established in Africa, in particular in a population without malaria immunity.

Methods. A study was conducted to evaluate the effectiveness of a 3-day course of therapy with quinine sulphate (10 mg/kg 8-hourly) followed by a single dose of sulfadoxine-pyrimethamine (SP) according to weight category, before discharge, for 133 hospitalised patients with uncomplicated *Plasmodium falciparum* malaria at Shongwe Hospital, Mpumalanga province, between February and July 1998. Study endpoints included clinical recovery and parasitological cure, including polymerase chain reaction (PCR) 42 days after initiating treatment.

Results. One hundred and thirty of 131 patients (99%) successfully followed up for 42 days demonstrated clinical and parasitological cure. The remaining patient, who had evidence of a recrudescent infection on PCR, was 1 of 61 patients who were still parasitaemic on discharge from hospital.

Conclusion. The abbreviated course of quinine therapy coupled with a single dose of SP for the treatment of non-severe hospitalised cases of *P. falciparum* malaria, in an area with demonstrated low levels of SP resistance, was highly effective. This approach has potential benefits, including reduced duration of hospitalisation, fewer quinine-associated adverse events and protection against the evolution of quinine resistance by limiting unsupervised quinine therapy in the community. It may, however, be prudent to document a negative blood film before discharge from hospital.

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Plasmodium falciparum malaria poses a significant health risk in the north-eastern border areas of South Africa. Mpumalanga province's lowveld region, which borders Mozambique in the east and Swaziland in the south, experiences seasonal malaria in the wet summer months from December to April. The population of approximately 850 000 people is consequently unlikely to have any immunity against malaria.

Malaria control in the area is by a combination of residual indoor house spraying with synthetic pyrethroids and early detection and treatment of cases at primary health care clinics. First-line therapy for malaria was changed from chloroquine to sulfadoxine-pyrimethamine (SP) in 1997 after an *in vivo* study found 48.4% resistance (RI, RII and RIII) to chloroquine, while a subsequent SP baseline *in vivo* study demonstrated a cure rate of 94.5% for uncomplicated cases treated with SP.[1]

Patients unable to tolerate oral medication and those deemed too unwell for outpatient care, particularly those with features of severe disease, as well as pregnant women and children under 2 years of age, are referred to the district hospital, Shongwe Hospital, for assessment, therapy and possible admission. As the majority of patients seen at the hospital are referred from clinics up to 70 km from the hospital and most patients have no access to personal transport, a liberal admission policy for malaria patients is adopted at the hospital. Admitted cases are treated with quinine therapy for 7 days, at the recommended dose, either orally or intravenously.[2]

During the peak of the malaria season, Shongwe Hospital occupancy rates frequently exceed 250%. This results in enormous demands on the limited resources available, with severe compromise of patient monitoring and nursing care that has contributed towards poor malaria treatment outcomes, including fatalities.[3] On the other hand, early discharge of patients on oral quinine therapy may jeopardise the continued usefulness of this important drug, as its side-effect profile discourages patient adherence.

This conundrum would be addressed if an abbreviated course of therapy was shown to be effective for those patients clinically well enough to merit earlier discharge.

METHODS

An uncontrolled study was conducted between February and July 1998 at Shongwe Hospital, Mpumalanga province, to evaluate the effectiveness of a 3-day course of therapy with quinine sulphate (10 mg/kg 8-hourly), by intravenous or oral route depending on patient tolerance, followed by a single dose of SP (according to weight category) before discharge for hospitalised patients with *P. falciparum* malaria. Study endpoints included clinical recovery and parasitological cure, demonstrated by temperature clearance, Giemsa-stained thick film (GTF) and polymerase chain reaction (PCR) 42 days after initiating treatment. Parasite counts were performed at the Shongwe Hospital laboratory on Giemsa-stained thin films, with quality control performed on all films at the provincial entomology and parasitology laboratory in Nelspruit. PCR for *P. falciparum* was also performed on filter-paper blood spots collected on all patients at study enrolment and 42-day follow-up.

All non-pregnant adults and children over 2 years of age sequentially admitted from the beginning of February with an episode of *P. falciparum* malaria documented by rapid malaria card test (immunochromatographic) and thin film parasitaemia greater than 800 asexual parasites/µl blood were considered for inclusion. Patients with a previous history of sulphonamide allergy were excluded. Baseline clinical, haematological and biochemical evaluation and daily clinical examination and parasite counts were performed while the patient was in hospital.

Patients appearing clinically well enough to be discharged after 3 days of quinine therapy, i.e. afebrile, ambulatory and where possible with a negative malaria film, were considered eligible for study inclusion. Informed consent was acquired. Of the 133 patients included, 2 patients were lost to follow-up and could not be traced for day 42 evaluation. One hundred and thirty-one patients (98%) were therefore successfully followed up.

The Mpumalanga Research and Ethics Committee provided ethical clearance for the study.

RESULTS

There were 74 female (56.5%) and 57 male (43.5%) patients included in the study. Age was accurately documented for 111 patients and ranged from 4 to 78 years, with a mean age of 20 years (median 16 years). Geometric mean parasite counts of the 131 study participants were 110 673/µl (825 - 1 162 500) at admission, 26 758/µl (0 - 675 000) at 1 day, 3 764/µl (0 - 78 750) at 2 days, and 687/µl (0 - 45 000) at 3 days after admission. Sixty-one patients (47%) were still parasitaemic at discharge from hospital.

At 42-day follow-up, all patients were clinically well and only 1 patient (0.8%) had malaria parasites demonstrated on PCR and blood film examination, with a parasite count of 1 800/µl. PCR confirmed a recrudescent infection rather than a new infection.

DISCUSSION

The high cure rate of 98% (130/133), based on intention to treat, of 3-day quinine therapy and single-dose SP demonstrated in this group of patients hospitalised with non-severe malaria is very encouraging. A literature review revealed three dated studies[4-6] in other areas that documented similarly high cure rates (95 - 100%) using a short course of quinine combined with a long-acting antimalarial, either SP or mefloquine, in areas with high levels of chloroquine resistance. These studies were also conducted in regions affected predominantly by seasonal malaria transmission at a time when SP or mefloquine were still effective against *P. falciparum* malaria.

The radical cure of *P. falciparum* requires therapeutic antimalarial levels to be maintained for at least three parasite life cycles, i.e. 6 days. Since the half-life of quinine is only 8 hours, this cannot be achieved by a short course of quinine alone. The effectiveness of short-course quinine therapy therefore requires combination with a second longer acting drug, such as SP, that is still effective against *P. falciparum*. Increased levels of SP resistance have been reported in other parts of southern Africa where SP has been used as first-line therapy, therefore it is imperative that regular *in vivo* testing of SP resistance is conducted to monitor the continued effectiveness of this drug.

The abbreviated regimen cannot be recommended for complicated malaria cases. In Papua New Guinea between 3% and 10% of children with cerebral malaria treated with short-course therapy failed treatment.[7]

The only patient to fail therapy in our study was 1 of 61 patients who remained parasitaemic at discharge, while none of the 70 patients with a negative blood film at discharge failed therapy. Although this finding was not of statistical significance (Fisher's exact $\chi^2 = 0.466$), this may simply reflect the low failure rate. A blood film performed at day 3 could identify patients possibly at greater risk of recrudescence; in these cases a longer course of quinine should be considered.

CONCLUSION

This study indicates the effectiveness of 3 days of quinine therapy coupled with a single dose of SP for the treatment of non-severe hospitalised cases of *P. falciparum* malaria, in an area with demonstrated low levels of resistance. It may, however, be prudent to document a negative blood film before discharge. This approach to therapy has vast potential benefits in Mpumalanga province and similar settings, including reduced duration of hospitalisation, fewer quinine-associated adverse

events and protection against the evolution of quinine resistance by limiting unsupervised quinine therapy in the community.

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SCREENING FOR PRIMARY ALDOSTERONISM — NORMAL RANGES FOR ALDOSTERONE AND RENIN IN THREE SOUTH AFRICAN POPULATION GROUPS

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Objective. To establish normal ranges for plasma aldosterone, renin and aldosterone/renin (A/R) ratio in South African normotensives under typical outpatient conditions, and to estimate the prevalence of primary aldosteronism (PA) among hypertensives in primary care settings.

Design and methods. One hundred and thirty-six normotensive subjects and 154 sex- and age-matched hypertensives at three primary care clinics had measurements of blood pressure, plasma creatinine, K^+, aldosterone, plasma renin activity, and spot urine for urinary Na^+/creatinine ratio. Medication was not withdrawn before testing.

Results. Mean plasma renin activity in black normotensive subjects (0.95 ± 1.25 ng/ml/h, mean ± standard deviation (SD)) was significantly lower than in white (2.09 ± 1.12 ng/ml/h; $P < 0.0001$) and coloured (1.81 ± 1.86 ng/ml/h, $P = 0.013$) normotensives. Mean plasma aldosterone in black normotensives (306 ± 147 pmol/l) was also significantly lower than in white (506 ± 324 pmol/l, $P = 0.0002$) and coloured (418 ± 304 pmol/l, $P = 0.0148$) normotensives. In hypertensives, there were no significant differences in renin or aldosterone levels between the three population groups. Urinary Na^+/creatinine ratios, an index of Na^+ intake, were not significantly different in the three population groups. None of the normotensives had an A/R ratio ≥ 1 000 plus aldosterone ≥ 750, while 7.1% of hypertensives exceeded these levels, suggesting that they are appropriate criteria for screening for PA.

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