Audit of failure rate of sulfadoxine/pyrimethamine combined with chloroquine to treat falciparum malaria at single fourteen-day follow-up.

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Summary

Objective.
To assess the failure rate of the present first line treatment regime for uncomplicated falciparum malaria of sulfadoxine/pyrimethamine combined with chloroquine.

Design.
A before-after study[1]

Setting.
Ndumo Clinic, Ingwavuma District, South Africa, October 2000
Study Group. 55 patients presenting to Ndumo clinic with uncomplicated malaria and malaria trophozoites visible on thin film.

Main outcome measures:
Trophozoite count on thick film at day 14.

Results.
15 out of 37 patients who returned for follow-up still had trophozoites on thick film. Symptoms of most patients at day 0 and day 14 were mild, parasite counts before and after treatment were low, and trophozoites were atypical.

Conclusions.
There appears to be an unacceptably high day 14 failure rate with the combination of sulfadoxine/pyrimethamine and chloroquine. The mildness of symptoms, low parasite counts and atypical trophozoites suggest immunity to falciparum malaria amongst the local population. With few antimalarials to chose from, the difficult question as to future treatment of uncomplicated malaria arises.

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Introduction

In 1988 sulfadoxine/pyrimethamine (SP) officially replaced chloroquine (CQ) as first-line treatment in malaria control in South Africa because of concerns about chloroquine resistance[2]. In northern KwaZulu-Natal medical officers at Mosvold, Manguzi, Bethesda and Mseleni hospitals used SP combined with CQ because of perceived benefit of chloroquine, whereas the Malaria Control Programme used SP alone to treat both self-presenting patients(passive cases) and cases detected through active surveillance. From January to April 2000 an in vivo study[3] of the efficacy of SP conducted by the National Malaria Research Programme at Ndumo Clinic, Ingwavuma District, KwaZulu-Natal, South Africa, showed failure of SP treatment in at least 61.2% patients by the end of 28 days. The 14 day failure rate was 50% of recruited (63/125), but 73%(63/86) of those who returned. In the absence of immediately available new first line anti-malarial drugs for uncomplicated malaria, SP combined with CQ was adopted as first line treatment for uncomplicated malaria throughout KwaZulu-Natal.

There have been few studies of SP combined with CQ. In a Cochrane review[4] McIntosh concluded that in areas where chloroquine is still effective, chloroquine in combination with

SP may make people feel better faster and improve sustained parasite clearance. Bojang et al[5], in a trial of SP alone versus SP with CQ in Gambian children, found SP with CQ to be more effective symptomatically, but no difference in parasite cure rate.

There has been a dramatic increase in malaria incidence in KwaZulu-Natal and South Africa since 1996. For example, at Ndumo clinic, Ingwavuma District, South Africa, (a satellite clinic of Mosvold Hospital, covering an area with the highest incidence of malaria in South Africa), cases detected increased from 637 in 1995, to 2 972 in 1998, and 17 420 in 1999. From January to May 2000 alone, 21 352 cases were detected at the clinic, requiring the aid of the South African Defence Force. In 1995, in South Africa, there were 5 992 notified cases of malaria[6] whereas from January to May 2000 there were 36 717 notified malaria cases[7]. With such large numbers of patients being treated, an audit of the failure rate of the treatment regime was desirable. A WHO protocol[8] for assessment of therapeutic efficacy of antimalarial drugs requires follow-up of patients on at least days 0,1,2,3,7 and 14. This requires substantial resources, and preventing patients dropping out is difficult. Department of Health Guidelines[9] recommend that a follow-up blood smear be taken after 2-3 weeks. This has not been implemented routinely in northern KwaZulu-Natal, due to numbers of patients and limited laboratory facilities. Applying the guidelines in the form of a single 14 day follow-up of a sample of patients was chosen as a quick and simple audit of the of the regime of SP and CQ combined, deviating little from routine management.

Table 1: Classification of Therapeutic Response[8]

Early treatment failure (ETF)	Patient develops one of the following conditions during the first three days of follow-up: • Development of danger signs or severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitaemia; • Axillary temperature> 37.5°C on Day 2 with parasitaemia > Day 0 count; • Axillary temperature > 37.5°C on Day 3 in the presence of parasitaemia; • Parasitaemia on Day 3 > 25 % of count on Day 0.
Late treatment failure (LTF)	Patient develops one of the following conditions during the follow-up period from Day 4 to Day 14: • Development of danger sings or severe malaria in the presence of parasitaemia on any day from Day 4 to Day 14, without previously meeting any of the criteria of early treatment failure; • Axillary temperature > 37.5°C in the presence of parasitaemia on any day from Day 4 to Day 14, without previously meeting any of the criteria of early treatment failure.
Adequate clinical response (ACR)	Patient shows one of the following conditions during the follow-up period (up to day 14): • Absence of parasitaemia on Day 14 irrespective of axillary temperature, without previously meeting any of the criteria of early or late treatment failure; • Axillary temperature < 37.5°C irrespective of the presence of parasitaemia, without previously meeting any of the criteria of early or late treatment failure.

The interval between date of infection with plasmodium falciparum and the time when parasites are detectable in the blood (the prepatent period) is 9-10 days[10]. This means that there is an increasing possibility that parasites present after day 14 may be due to reinfection rather than drug resistance. After 14 days techniques such as polymerase chain reaction are needed to distinguish between resistant malaria and reinfection. A blood film at day fourteen would be expected to provide useful information regarding the combined early treatment failure (ETF) and late treatment failure (LTF), as well as the proportion of patients showing adequate clinical response (ACR) to the therapeutic regime (see table I).

Study Population and Methods

Pre-study calculation of sample size

Sample size was calculated according to statistical considerations in a World Health Organisation protocol[8] using a system called the Double Lot Quality Assurance method. This system is designed to allow identification of communities in which prevalence of resistance is above a critical level, with small sample sizes. Taking a 25% failure rate to be definitely unacceptable, but 10% or less definitely acceptable, a sample size of 42 is sufficient to detect a 25% failure rate with a probability of 0.05 of erroneously concluding a failure rate of less than 10% (type I error), whilst being 80% sure of not erroneously concluding there to be a 25% failure rate when it is really less than 10% (type 2 error). Using this method and applying the given thresholds, 5 or less treatment failures could be considered acceptable, but more than 5 would be unacceptable. To allow for drop-outs, 55 patients were invited to return for follow-up.

In October 2000, over six working days, 89 self-presenting patients at Ndumo clinic, diagnosed as suffering malaria by positive immunochromographic test (KAT-Quick Malaria Rapid Test for Plasmodium falciparum – Cape Biotech (Pty) Ltd), were asked if they would be prepared to return for a two week check. Patients were assessed by a medical officer, and those with severe or complicated malaria, pregnant women, patients aged under 16 years and patients treated for malaria during the previous two weeks were excluded from the audit. Children under 16 were excluded so that all patients could receive exactly the same regime for simplicity, while other exclusions on clinical grounds were treated in hospital with quinine, according to standard practice. 87/89 patients were willing to return for follow-up at 14 days. Previous experience had shown that patients with more strongly positive rapid tests were more likely to have visible parasites on thin film, so there was a selection tendency to invite those with more strongly positive rapid tests. Thick and thin blood films were taken, and thin films read immediately after staining. Thick films required 24 hours to dry and so could not be read immediately. Only those who were thin film positive were asked to return for repeat blood smears at two weeks, to ensure that a comparison of parasite counts could be made.

The films were examined by a medical technologist from KwaZulu-Natal laboratory services. Thin films were air-dried, fixed with methanol, stained with 10% Giemsa rinsed with tap water, air-dried and examined using a 100x oil objective. Thick blood films allowed 24 hours to dry and then were stained with 10% Giemsa (5ml Giemsa diluted with 45ml phosphate buffer) for 10 minutes, rinsed with tap water, air-dried and observed with 100x oil objective. Malaria parasites were counted in conjunction with 300 white cells. The number of parasites was multiplied by 25 to estimate the number of parasites per microlitre of blood. Patients were given the usual adult treatment for uncomplicated malaria at Ndumo Clinic, which is given in table II.

All patients were told to return immediately should their condition deteriorate.

The Medical Superintendent of Mosvold Hospital accepted the study as an audit of current practice through the application of Department of Health guidelines.

Table II: Treatment regime for uncomplicated malaria at Ndumo Clinic

Sulfadoxine 500mg/pyrimethamine 25mg (fansidar - Roche)	3 tablets
Chloroquine sulphate 200mg (nivaquine - Rhone-Poulenc Rorer)	4 tablets
Followed by	
Chloroquine sulphate 200mg	2 tablets per day for 3 days to take at home

Table III: Results of follow-up smear at Ndumo Clinic, Oct 2000

Patients enrolled	55
Day 14 thick film negative	19
Day 16 thick film negative	1
Day 17 thick film negative	2
Total negative follow-up	22(40%)
Day 14 thick film positive	14
Day 17 thick film positive	1
Total follow-up thick film positive	15(27%)
Lost to follow-up	18(33%)

Results

56 patients had parasites visible on thin film. One patient left the clinic before the result of his thin smear, so 55 were asked to return for follow-up blood smears at day 14. Two patients who were negative at follow-up had been inadvertently retreated with SP and CQ at Ndumo clinic without medical referral; one received repeat treatment after seven days, and the other after 11 days. The results may be summarised as in Table III:

If it were assumed that all those who failed to return were parasite negative, and that the failure rate was really 15/55(27%) which is the best possible scenario for the regime, then the 95% confidence interval for the follow-up failure rate would be between 15% and 39%.

10 patients (one being the day 17 result) with parasites on thick film at follow-up showed a raised parasite count compared to day 0, while in 5 patients the parasite count was decreased.

Parasite counts were low: 49/55 patients had day 0 parasitaemia of less than 1000 trophozoites per microlitre. 6/55 day 0 parasite counts were between 1000-2000, the highest

count being 1575 trophozoites per microlitre. The highest follow-up count was a patient at day 14 with a count of 1500 trophozoites per microlitre. Thin films examined while the patient waited, only detected parasites in two follow-up patients.

The trophozoites in all but one patient were noted to be atypical, and not the typical plasmodium falciparum ring forms. Gametocytes were seen in one patient. Neither the patient with typical ring forms, nor the patient with gametocytes returned for follow-up.

The mildness of the presenting symptoms was notable. Of 76 patients initially considered for audit, whose temperatures were recorded in trial notes, 59 (78%) patients were apyrexial with temperatures of 37°C or less. Only one patient had a temperature above 37.9°C and that patient was admitted for treatment with quinine. Of 33 follow-up temperatures recorded, only one patient had pyrexia, with a temperature of 37.2°C.
Of interest is the observation that although 32/87 patients were excluded from the audit on account of being thin smear negative, thick smears only failed to see parasites on 2/76 thick smears (thick smears of patients not invited back were not kept for counts at the start of the audit).

Conclusions

Although 18/55 (33%) patients were lost to follow-up, this audit demonstrated that 15/55 (27%) patients failed to clear parasites at 14 days with SP/CQ combined. Despite the patients lost to follow-up, 15 failures from 42 or less patients well exceeds the 5 failures which would be considered the acceptable upper limit, assuming a 25% failure rate to be unacceptable, but less than 10% acceptable. As the proportion of failures amongst those who did return was 15/37 (41%), it is likely that the true failure rate is higher than 27%, which would be considered by most authorities to be unacceptably high, and necessitate the introduction of alternative first-line antimalarial therapy. Since completion of this audit Coartem™ tablets (20mg artemether and 120mg lumefantrine – Novartis South Africa (PTY) Ltd) have been introduced as the recommended treatment for uncomplicated malaria in KwaZulu-Natal[11].

The mildness of the symptoms, low parasite counts, and unusual appearance of trophozoites raise the question as to whether patient immunity is now having a major influence on the nature of the illness in northern KwaZulu-Natal.

A single fourteen-day follow-up audit is simpler to implement than protocols requiring at least five follow-up patient visits[8]. It may provide useful information as to the combined early treatment failure and late treatment failure of an established antimalarial regime, as well as indicating the proportion of patients showing adequate clinical response.

Thin film is less sensitive than thick smear having a smaller volume of blood per microscopic field[12] and excluded a number of patients unnecessarily from the audit. Future audits should not use thin smear to exclude patients from audit follow-up.

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